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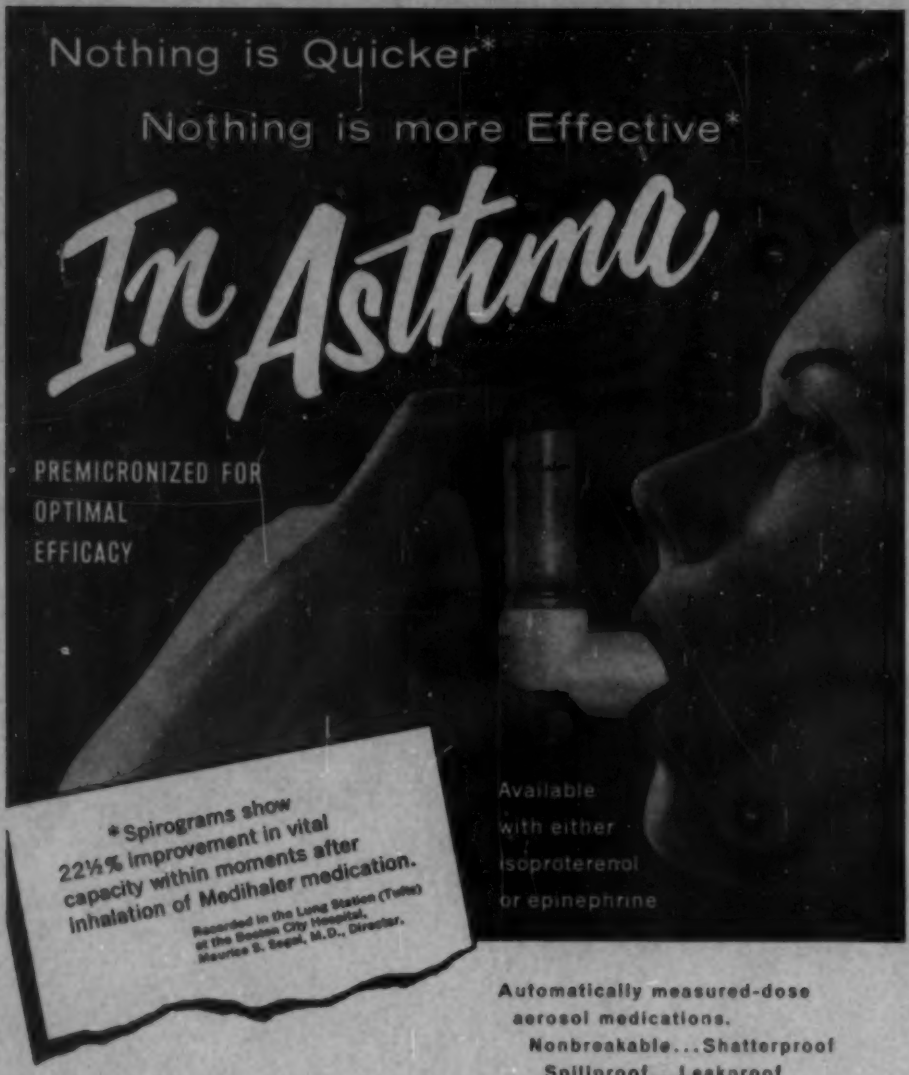
DECEMBER 1959

DISEASES of the CHEST

OFFICIAL PUBLICATION

Silver Anniversary Year

26th Annual Meeting
Miami Beach, Florida, June 8-12, 1960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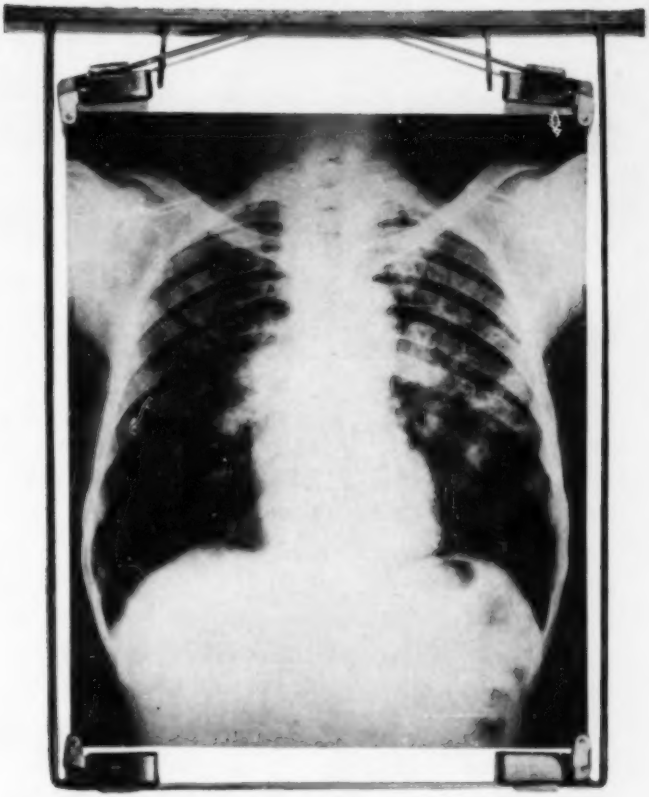

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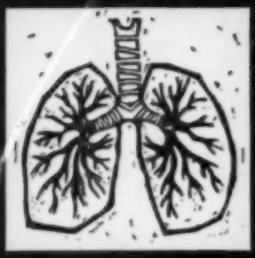

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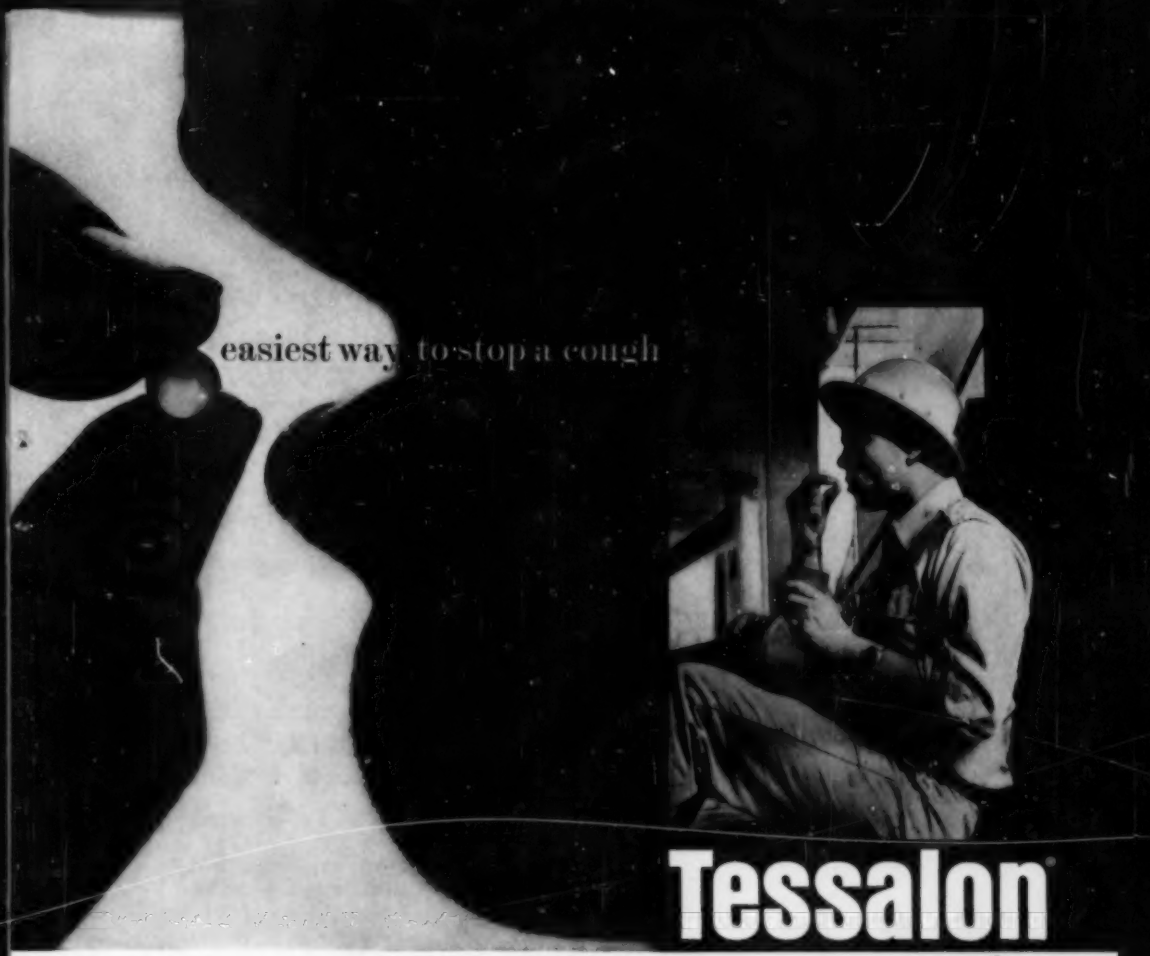

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1. Shane, S. J., Krzyski, T. K., and Copp, S. E.: Canad. M. A. J. 77:600 (Sept. 15) 1957.

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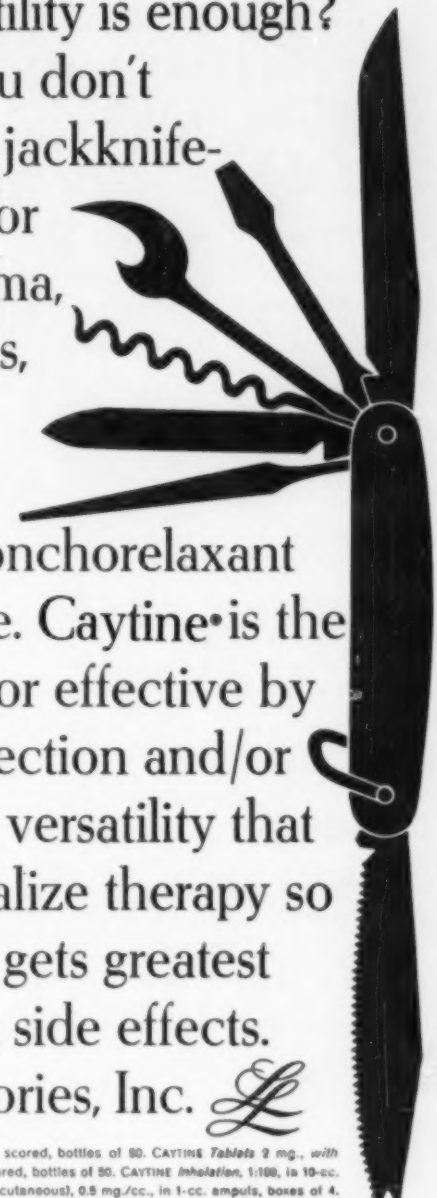

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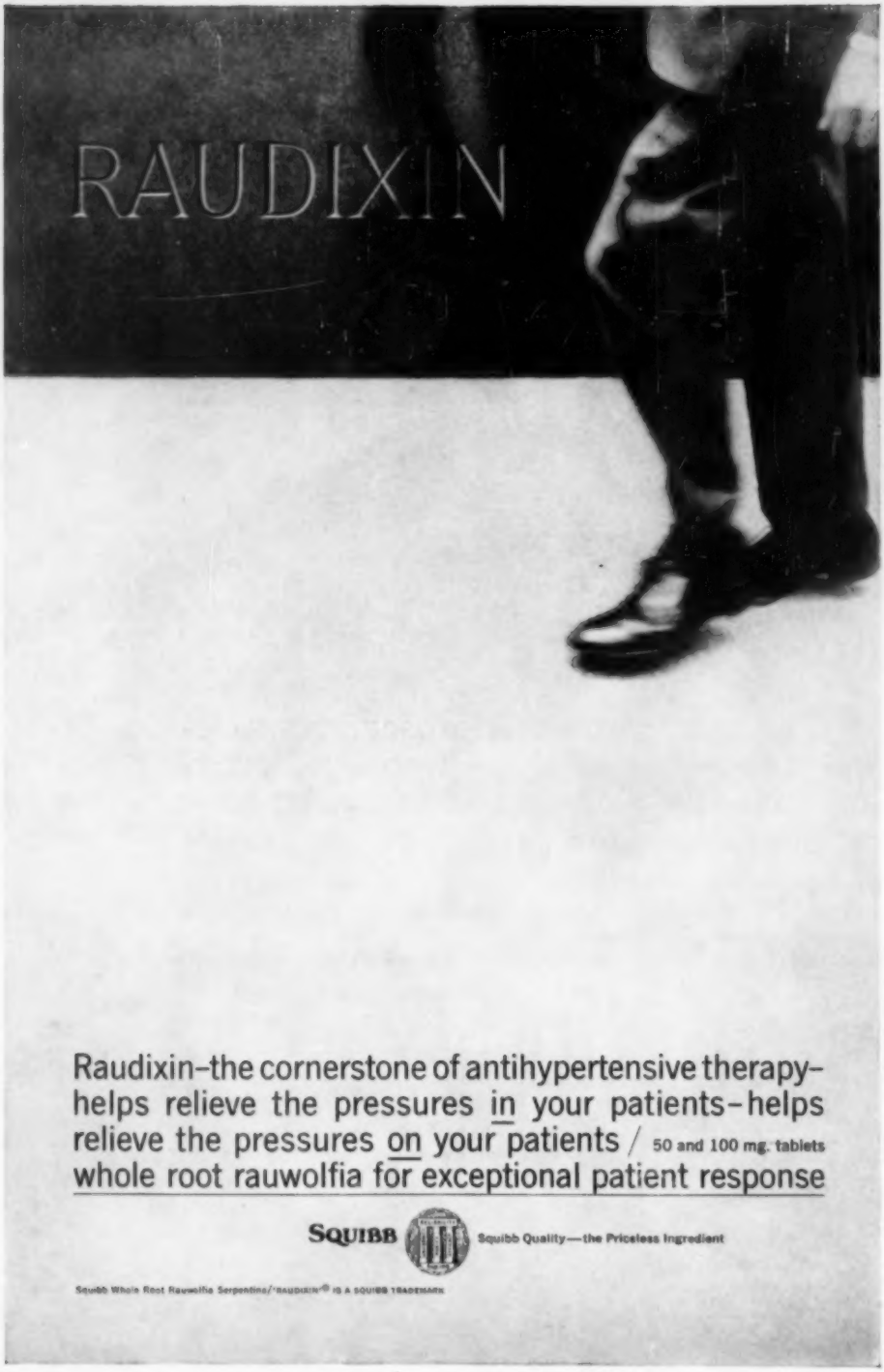

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Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please .....

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Inje*
bacteria resistant to it also

A A very good question, but
in almost two years of clin
treatment of infections fo
the emergence of KANTRE
lations has not been a pro

Q *My impression is that* KAN
cin. Isn't that so?

A Indeed not. The only thi
have in common is a simi
Otherwise, they're very di
chemical structures; the to
less than that of neomycin
Injection is practical for s
tinely, while neomycin is

Q *You mean that* KANTREX
nephrotoxicity of neomyci

A Precisely. It's true that
used, urinary casts – even
scopic hematuria – may
hydrated patients, but th
gressive damage to the kid
disappear on adequate h
therapy.

Q *Then why do you recomm*
tients with renal impairme

A Because renal impairment
lation of KANTREX in the b
doses are administered. Si
creted entirely by the kidn

x Injection, won't that help make it also?

n, but it is reassuring to note that of clinical use of KANTREX for the ons for which it is recommended, ANTREX-resistant bacterial popu- a problem.

t KANTREX *is just another neomy-*

ly thing KANTREX and neomycin a similar antimicrobial spectrum. ery different: they have different the toxicity of KANTREX is "much mycin"[14]; and clinically, KANTREX l for systemic administration rou- cin is not.

NTREX *Injection doesn't have the omycin?*

that when KANTREX Injection is - even slight albuminuria or micro- may appear, especially in poorly but this does not reflect any pro- he kidneys. These signs promptly ate hydration or termination of

ecommend reduced dosage in pa- pairment?

rment causes an excessive accumu- the blood and tissues, when usual ed. Since KANTREX Injection is ex- e kidneys, renal impairment leads to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus, A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX's *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms... rapid acting... does not encourage development of bacterial resistance... is well tolerated in specified dosage... and has not caused any blood dyscrasias.

KANTREX® CAP

for local gastroint
not for systemic i

Q *Why can't I use* KANTREX *Capsu*
cation?

A Because there is only negligible a
from the gastrointestinal tract.[3,
cannot provide effective blood le

Q *Then what are* KANTREX *Capsu*

A Preoperative bowel sterilization
of intestinal infections due to
organisms.

Q *I've been using neomycin for pr*
lization. Why should I switch t

A Because KANTREX has been rate
mycin" for this purpose.[4] It pro
factory control of coliforms, cl
and streptococci; yeasts do not
centrations of the drug are ex
nausea, vomiting or intestinal ir
observed.[5,6]

Q *What advantages do* KANTREX C
treatment of intestinal infectio

A A high degree of effectiveness
pathogens responsible for such i
Shigella, Staph. aureus, E. coli
tolytica. Moreover, their use has
of any side effects."[31]

APSULES

trointestinal therapy...
mic infections

Capsules for systemic medi-

gible absorption of KANTREX
ract.[3,5,6,8,28,34] Thus, capsules
lood levels.

Capsules used for?

zation, and local treatment
lue to kanamycin-sensitive

for preoperative bowel steri-
vitch to KANTREX *Capsules?*

en rated as "superior to neo-
It provides rapid and satis-
ms, clostridia, staphylococci
lo not proliferate; stool con-
are exceptionally high; and
inal irritation have not been

TREX *Capsules offer me in the*
fections?

veness against most of the
such infections: *Salmonella*,
E. coli and *Endamoeba his-*
se has been "remarkably free

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS
Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE
Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY
When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION
KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS
Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY
Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE
For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION
Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY
KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

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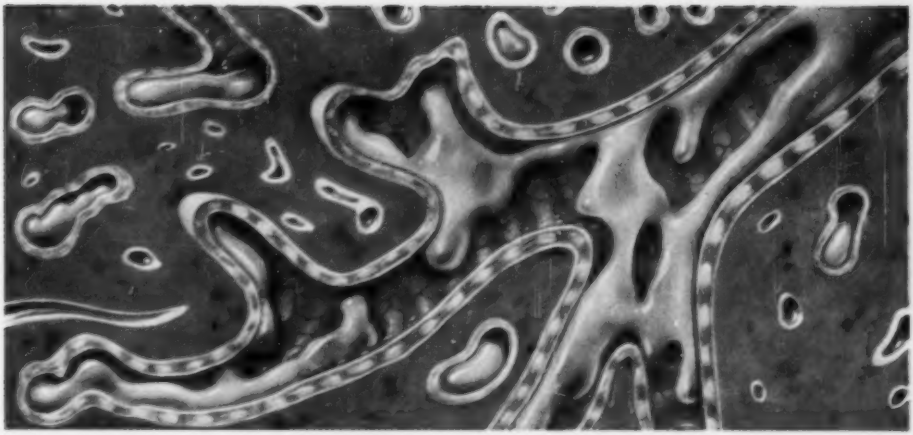

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greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (*Activity* level is the basis of comparison—not quantitative blood levels—since action upon pathogens is the ultimate value.*) Provides significantly higher serum activity level . . .

with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

unrelenting peak antimicrobial attack

The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline... for greater physician-patient benefit

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1 mg. Tablets

STELAZINE*

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For b.i.d. administration

FOR ANXIETY—
PARTICULARLY WHEN EXPRESSED AS APATHY,
LISTLESSNESS AND EMOTIONAL FATIGUE

often effective where other agents fail

*

enthusiastic patient acceptance

*

fast therapeutic response with very low oral doses

*

convenient b.i.d. administration

*

side effects usually slight and transitory

*Trademark

Clinically evaluated, before introduction, in over 12,000 patients

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UNUSUALLY EFFECTIVE IN RELIEVING ANXIETY IN APATHETIC, EMOTIONALLY FATIGUED PATIENTS

'Stelazine' is a new long-acting psychotherapeutic agent that can help you to bring prompt relief to many of your patients whose anxiety is expressed as apathy, listlessness and emotional fatigue.

Clinical studies in over 12,000 patients have shown that 'Stelazine' is outstanding among agents in its class because it not only relieves agitation and tension, but also *restores normal drive* in many patients who are apathetic due to anxiety.

These studies have also shown that 'Stelazine' is effective in low b.i.d. dosage (2 to 4 mg. daily) and that it is often effective in patients who have failed to respond to meprobamate, prochlorperazine, phenobarbital, mepazine, chlorpromazine, or promazine.

RECOVERY OF NORMAL DRIVE IN APATHETIC PATIENTS

Clinicians report that with 'Stelazine' most apathetic, listless and emotionally fatigued patients regain an alert, more confident outlook. This frequently results in increased mental and physical activity. For example:

> Patients' "spirits brightened and initiative and interest picked up considerably in contrast to their pretreatment inertia."[1]
>
> 'Stelazine' "seemed to have a capacity to restore normal drive in conditions characterized by decreased motor activity and mental apathy."[2]

ADDITIONAL INFORMATION will reach you by mail or through your S.K.F. representative. We hope you'll decide that 'Stelazine' deserves an early trial. Smith Kline & French Laboratories, Philadelphia.

REFERENCES: 1. Gearren, J.B.: Dis. Nerv. System *20*:66 (Feb.) 1959. 2. Margolis, E.J., et al.: Scientific Exhibit at 12th Clinical Meeting of the American Medical Association, Minneapolis, Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: Clin. Med. *6*:387 (Mar.) 1959. 5. Tedeschi, D.H., et al.: in *Trifluoperazine: Clinical and Pharmacological Aspects*, Philadelphia, Lea & Febiger, 1958, pp. 23-33.

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ARE YOUR PATIENTS GETTING THE OXYGEN CONCENTRATION PRESCRIBED?

AUTOMATIC CONTROL UNIT DEVELOPED BY O.E.M. CORPORATION

Recent medical research has emphasized the importance of accurately controlling oxygen concentration in oxygen tents.

Retrolental Fibroplasia in infants and respiratory acidosis in older patients with pulmonary fibrosis are often caused by indiscriminate use of high oxygen concentrations. On the other hand, high concentrations of 50% to 60% are imperative for many cardiac patients. Research not yet published will point out the need to administer oxygen in controlled dosage like any drug.

CURRENT OXYGEN CONTROL METHODS UNSATISFACTORY

Control of oxygen concentrations in tents has always been difficult, requiring frequent analysis with an oxygen analyzer plus constant adjustment of the flow. Many factors can affect the concentration: Leaks in the tent, poor canopy tucking, inadequate liter flows, failure to use flushing procedures. Even the most elaborate inhalation therapy department cannot afford the necessary technicians to make certain proper oxygen concentrations are maintained.

OXYGEN TENT THERAPY STILL MOST COMFORTABLE

The oxygen tent is the most comfortable method for administering long-term oxygen therapy. There are no encumbering masks, cannulae or catheters to disturb the patient. He retains freedom to move, sit up, talk and eat. Oxygen tent therapy is also the method of choice, or necessity, with delirious patients, in head wound cases and where a modulated temperature is desired during the summer.

NEW ELECTRONIC UNIT ASSURES CONSTANT OXYGEN CONTROL

The O. E. M. Corporation, leader in the development of oxygen tents, has completed a long-term research program designed to solve the oxygen control problem. Result is a new oxygen tent that maintains a preset oxygen concentration automatically, electronically, without attendance.

The desired percentage of concentration is set on a meter – just like the desired temperature. The electronic control unit automatically adjusts the flow of oxygen to maintain the prescribed concentration. This new oxygen concentration control unit, called the O.E.M. AUTOMATIC MECHANAIRE, is perhaps the most important advance in oxygen tent therapy since the tent was invented.

HOW THE CONTROL UNIT WORKS

A sample of the atmosphere under the canopy is constantly being drawn into a continuous oxygen analyzer. Every 15 seconds, the concentration is monitored. The control unit maintains the concentration within a 6% range.

When the monitor finds the concentration below the range, oxygen at 40 liters a minute is flushed into the tent. There is a visual indication that oxygen is flushing into the tent. Oxygen continues to flush into the unit until the concentration is within the preset range. When the monitor discovers this, the flow of oxygen drops to a maintenance flow of 12 liters per minute . . . visually indicated on the control panel. If the oxygen concentration rises above the desired range, maintenance flow is cut off and air is flushed into the tent to bring the concentration down.

AUTOMATIC SAFETY VALVE PROTECTS PATIENT

Note that when a lower concentration is desired, it is not achieved merely by shutting off the oxygen flow. On the O.E.M. *AUTOMATIC* MECHANAIRE, an automatic air safety valve starts drawing room air into the tent as soon as the oxygen flow drops below 6 liters per minute. There is no danger of carbon-dioxide build-up because either air or oxygen in substantial quantities is being drawn into the canopy constantly, washing out the carbon-dioxide.

CLINICAL TESTING SHOWS ADVANTAGES

Under clinical conditions, the oxygen concentration in a new O.E.M. AUTOMATIC MECHANAIRE was brought up to 50% from room air in 10 minutes by electronic control. In comparison, more than an hour was required to bring a tent up to 50% concentration at the normal flow rate of 10-12 liters per minute.

The new O.E.M. AUTOMATIC MECHANAIRE maintained a 50% oxygen concentration for a 24-hour period under clinical conditions...on the maintenance flow of 12 liters per minute 96% of the time and on the flush cycle only 4% of the time. It maintained 60% oxygen concentration under clinical conditions on the maintenance flow of 12 liters of oxygen per minute for 90% of the time . . . and on flush for 10% of the time. Conclusive evidence that the new O.E.M. AUTOMATIC MECHANAIRE can maintain high concentrations of oxygen for therapeutic purposes with an economical consumption of oxygen.

CONTROL UNIT AVAILABLE FOR MODEL #50 MECHANAIRES

The O.E.M. AUTOMATIC MECHANAIRE including tent and electronic concentration control unit sells for $1,500. The control unit alone – which fits any model #50 or #55 Mechanaire – is $850. Control units for model #30 Mechanaires and tents not manufactured by O.E.M. are available on special order at slightly higher prices.

Additional information on the new O.E.M. AUTOMATIC MECHANAIRE may be obtained by writing O.E.M. Corporation, East Norwalk, Conn.

For the first time

CONVENIENCE and ECONOMY

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TERRAMYCIN
(brand of oxytetracycline)

INTRAMUSCULAR SOLUTION

Initiation of therapy in **minutes after diagnosis** with new, ready-to-inject Terramycin Intramuscular Solution provides maximum, sustained absorption of potent broad-spectrum activity.

...and for continued, compatible, coordinated therapy

COSA-TERRAMYCIN
(oxytetracycline with glucosamine)

CAPSULES

Continuation with oral Cosa-Terramycin every six hours will provide highly effective antibacterial serum and tissue levels for prompt infection control.

The unsurpassed record of clinical effectiveness and safety established for Terramycin is your guide to successful antibiotic therapy.

Supply:
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100 mg./2 cc. ampules | 250 mg./2 cc. ampules

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125 mg. and 250 mg.

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125 mg./5 cc., 2 oz. bottle

Cosa-Terramycin Pediatric Drops – peach flavored,
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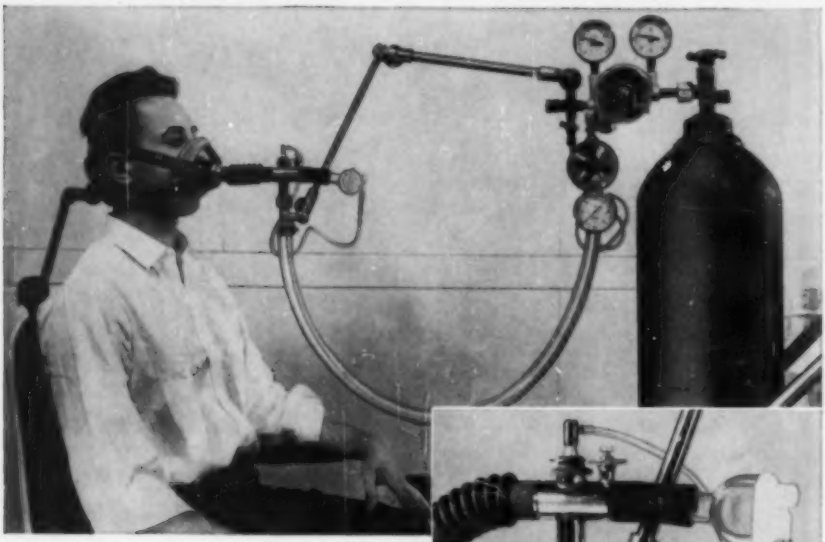

The M-S-A Pulmonary Ventilator provides effective pressure breathing therapy in combination with aerosol therapy.

Clinically proven, this instrument effectively distributes aerosols such as bronchodilators, detergents and bacteriostatic agents throughout the respiratory tract. Equipped with new easy-to-clean, maintenance-free exhalation valve assembly. Operates from either a piped system or an oxygen cylinder.

Ease of operation permits quick, efficient application in hospitals, doctors' offices or in patient's home under physician's directions. Produces dramatic relief for most patients suffering from Emphysema, Asthma, Silicosis and similar diseases. May we *demonstrate* these and other advantages of this unit?

Note: the new M-S-A Pulmonary Ventilator provides both dilution and 100% oxygen. It is sold only on the prescription of a licensed physician or on the order of properly qualified hospitals and other institutions.

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safely controls the "target symptoms" of emotional stress with the smallest effective dosage of any neuroleptic* agent (0.25 mg. b.i.d.)

•

virtually free from side effects at the recommended dosage level

•

a significantly wider spectrum of "target symptoms" is amenable to therapy

•

onset of action is rapid; duration of effect is prolonged

*Neuroleptic "The term 'neuroleptic' implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on affective tension that distinguishes this response from that to hypnotic drugs. The terms 'ataractic' and 'tranquillizer' are descriptively impressive, but fail to convey what seems psychopharmacologically unique."

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in everyday office practice

"Fluphenazine (PERMITIL) the latest and most potent phenothiazine tranquilizer was administered from 3 to 20 months to 200 ambulatory and hospitalized patients representing a full spectrum of diagnostic classifications including psychosomatic disorders. Fractional doses of this drug rapidly produced improvement in 74% of these patients while causing a minimum of sedative, autonomic and endocrine effects which disappeared as treatment continued. . . . Patient acceptance of this compound was excellent because its prescription facilitated rather than interfered with the efficient performance of daily tasks. The physician who masters the art of fluphenazine use can treat a widened spectrum of target symptoms, safely and effectively."[2]

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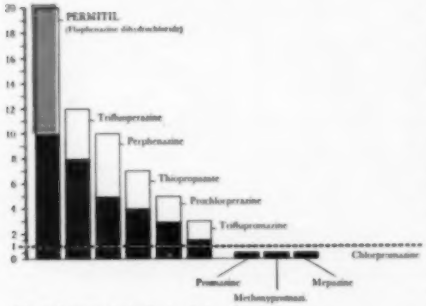
for the first time,
a phenothiazine
anti-anxiety agent
PERMITIL
designed specifically for
everyday office practice

A Factor to Consider in Phenothiazine Therapy

"The more potent the phenothiazine derivative the fewer the side effects it produces, because less of the chemical is needed to effect behavioral and therapeutic changes."[2]

The Relative Therapeutic Potency
of Various Phenothiazines



Adapted from Ayd, F. J., Jr.[3]

Clinical Results with* PERMITIL—*a Phenothiazine. In one study[2] covering a two-year period, PERMITIL was prescribed for 200 patients who were disabled primarily by anxiety and its somatic, emotional, mental and behavioral effects.

"After 3 months of fluphenazine (PERMITIL) therapy, 74% or 148 of the 200 patients evaluated were improved. . . . Thus the therapeutic effectiveness of fluphenazine (PERMITIL) is somewhat better than that of other potent tranquilizers."[2]

The relatively minor somatic reactions occurred in the early weeks of treatment with doses above 2 mg. daily. They seldom required other medication to counteract them and disappeared as the maintenance dose was established. At dosage levels under 3 mg. a day, extrapyramidal side effects were minimal. Results of extensive laboratory tests on 130 patients disclosed that "fluphenazine (PERMITIL) administered over 3 to 18 months had no deleterious effect on the blood, liver or kidney in these patients."[2]

The Importance of* PERMITIL *in Everyday Practice. "In contrast to other phenothiazines, it (PERMITIL) mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."[2]

How to Prescribe* PERMITIL.** For most adults: One 0.25 mg. tablet b.i.d. (taken morning and afternoon). In refractory cases: Two 0.25 mg. tablets b.i.d. Total daily dosage in refractory cases should not exceed 2 mg., in divided doses. Dosage for children has not been established. ***Complete information concerning the use of this drug is available on request.

Available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J., Jr.: Fluphenazine: its spectrum of therapeutic application and clinical results in psychiatric patients, Current Therapeutic Research, 1:41 (Oct. 15) 1959. 3. Ayd, F. J., Jr.: The current status of major tranquilizers, in press.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

a clinical and experimental study

CHEMICAL QUANTITATION OF EPINEPHRINE AND NOREPINEPHRINE IN PLASMA

Their Plasma Concentration in Hypertension, Shock, and Mental Disease, With Some Metabolic Studies

By

WILLIAM MUIR MANGER, B.S., M.D., Ph.D.
Department of Medicine
College of Physicians and Surgeons
New York City, New York
Formerly, Fellow in Medicine
Mayo Foundation, Rochester, Minnesota

KHALIL G. WAKIM, M.D., Ph.D.
Section of Physiology
Mayo Clinic
Rochester, Minnesota

JESSE L. BOLLMAN, M.D.
Section of Biochemistry
Mayo Clinic
Rochester, Minnesota

"This is more an introduction to a man and an idea than to a book. It indicates how, I believe, the combination of an idea, a good mind and untiring resolution seasoned with patience and time and the essential ingredients for good research can produce a work that is outstanding."—*from the Introduction by EDGAR VAN NUYS ALLEN, M.D., Past President of the American Heart Association, Rochester, Minnesota.*

A successful and different approach! The authors present a modification of a fluorescent technique for chemically quantitating epinephrine and norepinephrine in plasma, pheochromocytomas, and cerebrospinal fluid. This fluorescent method appears **reasonably simple, highly sensitive** and **fairly specific** and **accurate.** It has proved of great aid in screening patients suspected of having pheochromocytoma. It also seems **admirably suited** for studying the effects of various forms of physiologic stress on the concentration of plasma pressor amines and for investigating some phases of the metabolism of epinephrine and norepinephrine.

THE DESIRABILITY OF USING THIS FLUORESCENT METHOD MORE EXTENSIVELY AS A CLINICAL AND RESEARCH TOOL SEEMS ESTABLISHED.

For those interested in a better understanding of the relationship of the pressor amines to

1. *Clinical and experimental hypertension*
2. *Experimental hemorrhagic or anaphylactic shock*
3. *Mental Diseas*

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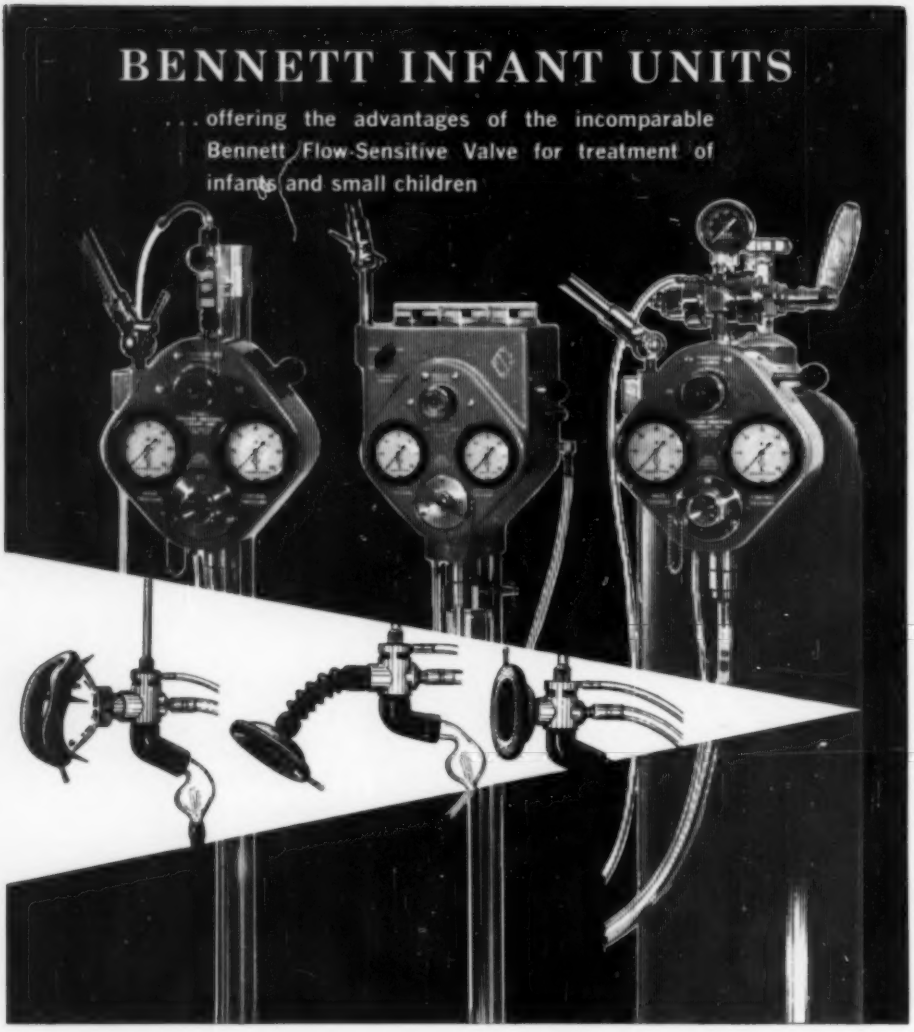

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DISEASES of the CHEST

VOLUME XXXVI DECEMBER, 1959 NUMBER 6

Primary Lymphosarcoma of the Lung

EMMETT R. HALL, JR., M.D. and BRIAN BLADES, M.D., F.C.C.P.

Washington, D.C.

Primary lymphosarcoma of the lung is rare. Like other lymphomatous diseases, the etiology of lymphosarcoma is unknown. Within the lung there are nests of lymphoid tissue about the bronchi and scattered throughout the parenchyma. It is generally agreed, that lymphosarcoma may remain confined to the lung for a relatively long period, enlarging by direct extension. In this respect it is similar to gastric lymphosarcoma. Growth may even extend across the interlobar fissure. The rich bed of mediastinal nodes is invaded by way of the peri-bronchial lymphatics as well as direct extension. Vascular invasion is infrequent, however tumor cells have been seen in these channels.[4, 8] Distant metastases occur, presumably by this route. Encroachment upon the adjacent bronchi causing stenosis or even obstruction is common. Involvement of the mucosa seldom occurs.

Grossly, the tumor is a reddish gray mass usually softer than bronchiogenic carcinoma. It may be well delineated, but often appears to blend into the surrounding lung. Atelectasis distal to the lesion is common. Sections of the tumor are gray and granular.

Microscopically, lymphosarcomas are composed of sheets or layers of lymphoblasts or lymphocytes. These cells are of rather uniform maturity and slightly smaller than the average lymphocyte. Infiltration into the lung is frequent. Mitotic figures are rare and difficult to recognize.

Sugarbaker[11] in 1940 reported 196 lymphosarcomas, only one of which had its origin in the lung. Since then there have been 26 additional cases recorded (Fig. 3). During the past 10 years at The George Washington University Hospital we have operated upon three patients with primary lymphosarcoma of the lung. These case histories will be presented as well as a brief review of the literature.

Case 1: A 61 year old white man, was admitted to The George Washington University Hospital on May 23, 1949 complaining of wheezing and sub-sternal pain of three weeks duration. He had an occasional cough productive of moderate amounts of mucus. Under his physician's care he received Achromycin 250 mgm. every four hours. Moderate improvement followed.

On admission to the hospital the patient appeared to be well-nourished and in good general health. There were ronchi audible throughout the chest with diminished breath sounds over the right lower lobe. No other significant abnormal finding was present.

The laboratory reported a normal hemogram and urinalysis. Serologic test for syphilis was negative. Total serum protein was 6.5 grams per cent with a reversal of the albumin globulin ratio.

On roentgenograms of the chest there was an opacity extending downward and outward from the right hilum. The left lung was not involved.

From the Department of Surgery, The George Washington University School of Medicine.

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On May 24, 1949 an ulcerating mass in the right main bronchus was seen through the bronchoscope. The tissue bled easily. Biopsy diagnosis was lymphosarcoma of the bronchus.

Thoracotomy was performed on June 1, 1949. The middle lobe was completely atelectatic. Careful palpation of the lung revealed nodular infiltrations throughout the middle lobe and the superior portion of the lower lobe. Neoplastic tissue engulfed the pulmonary artery and main bronchus. The patient was considered inoperable and a biopsy was taken from the tumor mass in the middle lobe. Pathologic diagnosis of lymphosarcoma of the lung was made.

After operation he had a septic temperature pattern for three days. He was given penicillin. On the fifth day after thoracotomy radiation therapy was begun. Radiation was administered to the left anterior and posterior chest. He was discharged on the 10th postoperative day, completing the course of radiation as an out-patient. On October 4, 1949, because of lumbosacral pain and 16 pound weight loss, he was readmitted. A general bone survey by roentgenogram revealed metastatic lesions involving the skull, spine and the left fifth rib. He expired in March 1950.

Case 2: A 49 year old white woman was first seen by her physician in July 1951 complaining of sharp chest pain of four days duration. She had an associated cough productive of small amounts of mucoid sputum. There was no history of hemoptysis.

X-ray films of the chest showed a homogenous density in the right lower lobe and a similar density in the inferior segment of the lingular division of the left upper lobe (Fig. 1). A previous film in October 1950 taken by the U.S. Public Health Service was considered normal. A tentative diagnosis of lipoid pneumonia was made.

Under her physician's care she received penicillin with remission of the acute episode. Since this time she had been seen at frequent intervals.

In May 1952 because of persistence and recent enlargement of the shadow in the right lung she was referred to the surgical service of The George Washington University Hospital.

On admission to the hospital the patient appeared to be well-nourished and younger than her stated age. There were occasional fine rales in the left lower chest posteriorly and increased tactile fremitus over the base of the right lung. No other significant abnormal findings were present.

Laboratory studies revealed a normal hemogram and urinalysis. Sputum cultures grew only gram positive cocci. Serologic test for syphilis was negative.

On May 28, 1952 right thoracotomy was performed. Careful palpation of the lung revealed a six centimeter mass in the right lower lobe extending across the oblique fissure into the right middle lobe. There was no evidence of enlarged hilar nodes. Biopsies were taken of the tumor mass and mediastinal nodes. The pathological report was lymphosarcoma of the lung and chronic mediastinal lymphadenitis.

Because of the infiltration in the lingula of the left lung, it was feared she had bilateral pulmonary lymphosarcoma. There was however, a history of habitual use of

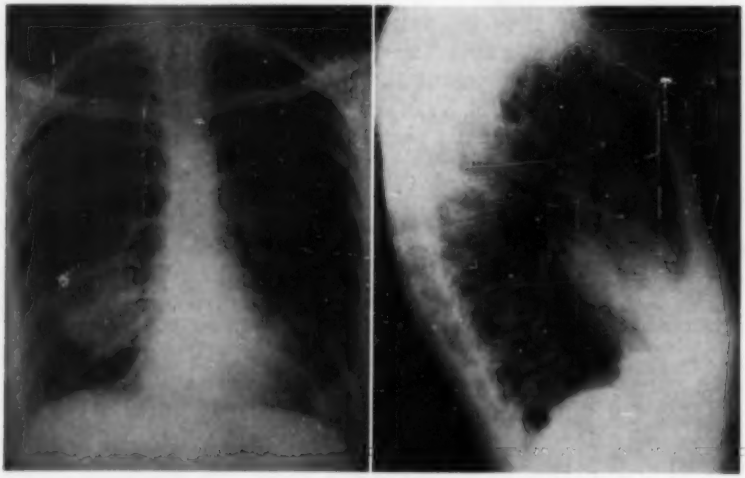

FIGURE 1A FIGURE 1B

Figure 1: PA and lateral x-ray film views of the chest showing a homogeneous density in the right lower lobe and a similar density in the lingular division of the left upper lobe.

oily nose drops over a long period of time. Moreover, the appearance of the lesions in both lungs on x-ray film was compatible with lipoid pneumonia. Accordingly, it was decided to use a test dose of roentgen therapy to the lesion in the lingula. Following radiation the shadow in the left lung remained unchanged. It was then considered to represent a pneumonic process.

Right pneumonectomy was done on July 21, 1952. On the 10th postoperative day she was discharged.

Pathological examination showed the lung to weigh 490 grams. The pleura was smooth, thin and had the usual anthracotic markings. In the medial aspect near the base of the lower lobe was a firm area six centimeters in diameter (Fig. 2). Cut sections of the area were gray, granular and meaty. The bronchi were dilated distally. The remainder of the lung was reddish gray and emphysematous. The bronchopulmonary lymph nodes were soft and black. Microscopically the tumor showed a heavy infiltrate of lymphocytes. In some areas the cells tended to form indefinite lymph follicles.

She has been seen at frequent intervals. To date she is well and has no evidence of recurrence or metastasis.

Case 3: A 70 year old white woman was admitted to The George Washington University Hospital July 9, 1953 for evaluation of a shadow in the left lung. Two weeks prior to admission she had seen her physician complaining of chills, fever, and cough. Penicillin had been given with moderate improvement.

On admission to the hospital she appeared to be in good health. Blood pressure was 190 systolic and 120 diastolic. A two centimeter nodule was palpable in the right lobe of the thyroid. No other significant abnormal findings were present.

Laboratory studies revealed a normal hemogram and urinalysis. Electrocardiogram was considered to be normal.

Roentgenograms showed an area of consolidation in the left upper lobe. A presumptive diagnosis of bronchogenic carcinoma was made.

On July 10, 1953 a bronchoscopy was done. The left main bronchus was 50 per cent contracted just below the left upper lobe orifice. This area was irregular and bled easily. Biopsies of the site showed chronic inflammation.

A right thyroid lobectomy and scalene node biopsy were done three days later. Pathological report was nodular goiter and negative lymph node.

Thoracotomy was performed on July 22, 1953. Exploration revealed a four by five centimeter triangular area in the left upper lobe which appeared red and atelectatic. Extending from this area toward the hilum was an irregular, hard tumor invading the mediastinal structures. The pulmonary artery and superior vena cava were surrounded by tumor. There was direct extension into the right mediastinum. The lesion was considered inoperable. Biopsies were taken from the tumor and mediastinal lymph nodes. The pathological examination was reported as lymphosarcoma of the lung and normal hilar lymph nodes.

After operation she made an uneventful operative recovery. On August 3, 1953 radio-therapy was begun. Metastasis evident, nitrogen mustard six milligrams intra-

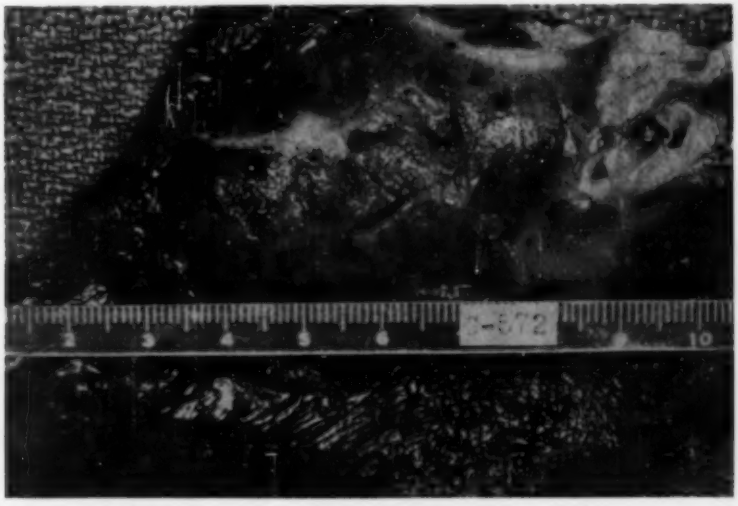

FIGURE 2: Gross specimen showing tumor area in right lower lobe.

TABLE I

Author	Age	Sex	X-Ray	Symptoms	Metastases	Bronchoscopy	Operation	Ratiation Therapy
Anlyan	63	M	4 x 4 cm. density R.L.L. (Discrete)	None	None	Neg.	Rt. Lower Lobectomy	Yes—For Recurrence
Beck and Reganis	47	F	Density R.L.L. (Discrete)	None	None	No	Rt. Lower Lobectomy	
Behrend*	59	F	L.L.L.	Yes	None	Neg.	Pneumo-nectomy	
Betts and Overholt*		M	R.U.L.		Yes		Inoperable	
Churchill	45	F	R.U.L.	None	None	Neg.	Rt. Upper Lobectomy	Yes
Grimes	45	F	Left Hilar Mass	Yes (Chest Pain)	None	Neg.	Pneumo-nectomy	
Grimes	68	F	L.L.L.	Yes, Cough, Hemoptysis, Dyspnea on Exertion, Wt. Loss	None	Neg.	Pneumo-nectomy	
Maier	50	M	L.U.L.	None	None	Neg.	Pneumo-nectomy	Yes Contra-Lat. Lesion
Ochsner and DeCamp*	66	M			Yes			
Ochsner and DeCamp*		M	L.U.L.		None		Lt. Upper Lobectomy	

Ochsner and DeCamp*	46	M	R.U.L.		None		Pneumo-nectomy	
Ochsner and DeCamp*	50	F		None			Pneumo-nectomy	
Pekelis*			L.U.L. (Discrete)	None	Yes	None		
Rose	75	F	L.U.L. (Wedge Shaped Density)	Yes (Pain, Fatigue, Malaise)	None	Pos. For Malignant Cells	Pneumo-nectomy	
Rose	38	F	R.U.L.	None	None	Neg.	Rt. Upper Lobectomy	
Cooley, McDonald and Clagett	46	M	Lt. Hilum	Yes (Cough, Fever)		Neg.	Lt. Upper Lobectomy	Yes
	67	F	R.U.L.	Yes (Fever, Chill, Cough, Pain)	None	Neg.	Rt. Pneumo-nectomy	Yes
	35	F	R.U.L. Rt. Mid-Lung Field	Yes (Cough, Sputum, Fatigue, Fever, Recurrent Flu)	Yes		Rt. Pneumo-nectomy	Yes
	64	F	Lingular Hilum	Yes (Cough, Dyspnea on Exertion, Wt. Loss, Pain)		Neg.	Lt. Pneumo-nectomy, Partial Pericardectomy	Yes

*Cited by other authors.

(Continued on Next Page)

Table I—Continued

Author	Age	Sex	X-Ray	Symptoms	Metastases	Bronchoscopy	Operation	Radiation Therapy
Sarokhan	70	M	Lingula	Yes (Cough, Hemoptysis)	None	Neg.	Lt. Upper Lobectomy	
Spatt and Grayzel	34	F	R.L.L. (Discrete Area of Density)	Yes (Cough, Hemoptysis)	None	Neg.	Rt. Upper Lobectomy	
Sugarbaker								
Touroff*			R.U.L.—5 cm. (Discrete)		None		Rt. Upper Lobectomy	
Dvoracek*	44	M	R.U.L.	None	Yes	Pos. Bronchial Washings		
Weissman and Christie	52	M	L.U.L.	Yes (Cough, Dyspnea on Extention, Wt. Loss)	None	Neg.	Pneumonectomy	
Willis	57	M	R.U.L.	Yes (Recurrent Pneumo.)	Yes		Rt. Upper Lobectomy	Yes
Fleming	57	F	Rt. Lung	Yes Hemoptysis	Yes			

*Cited by other authors.

venously for four doses was given in March 1955 without depression of the bone marrow. She was then maintained on oral HN$_2$ until August 1955. At this time she was given triethylene thio-phosphoramide (Thio-Tepa). This served only as palliation. Deterioration continued and she expired September 14, 1955.

DISCUSSION

Lymphosarcoma of the lung does not appear to have any sex or age distribution. The youngest patient was 34 years of age and the oldest 75 years, the average being 53 years of age.

Symptoms when present were those of a pneumonic process, characterized by cough, fever, dyspnea on exertion, chest pain and occasionally hemoptysis. Often the only finding was a density in the lung found on chest x-ray film. Radiologically these tumors may give a variety of impressions. Most frequently the x-ray film, diagnosis of pneumonia is made because of consolidation of a lobe or entire lung. Instances of discrete lesions have been noted, the smallest of which has been four centimeters in diameter.[1] Because of this variable one should always be suspicious of a discrete lesion or "pneumonia" which does not clear with adequate therapy.

Unfortunately, history, physical, and laboratory tests are of little benefit in the diagnosis of lymphosarcoma. Bronchoscopy may show stenosis or obstruction of a bronchus. There has been but one instance of diagnosis by bronchial biopsy (Case 1). In two patients reported in the literature, a diagnosis of malignant cells was made by cytological examination of bronchial washings. Patients with lymphosarcoma confined to the lung, thoracotomy with biopsy and pathological study is the only positive means of arriving at a diagnosis.

Churchill[5] was one of the first to employ resectional therapy for pulmonary lymphosarcoma. Of the 30 cases in the literature 22 were amenable to excision. Of this number 12 pneumonectomies and 10 lobectomies were done. Four patients were considered inoperable and three reported at autopsy.

Roentgen therapy has been used as an adjunct in the treatment of eight patients. Maier[7] reported complete resolution of a subsequent lesion in the contralateral lung, following which the patient lived 13 years and nine months before succumbing to coronary thrombosis. Some feel that radiation should always be utilized regardless of the extent of the lesion or the thoroughness of the operation. Chemotherapeutic agents were administered in Case 3 for palliative purposes. As yet the use of these drugs in pulmonary lymphomas cannot be evaluated. There are, however, some encouraging reports of lymphomas in other regions responding favorably to this type of therapy.

SUMMARY

Three patients with primary lymphosarcoma of the lung have been presented. From this small series one would believe that the prognosis in resectable pulmonary lymphosarcoma is more promising than bronchiogenic carcinoma. The extent of resection must depend on the location of the lesion and age of the patient. There are varying views on the use of roentgen therapy. Some feel it should always be used, while others use it only for recurring lesions.

RESUMEN

Se han presentado tres enfermos con linfosarcoma primario del pulmó. Según esta pequeña serie, parecería que el pronóstico del linfosarcoma resecable pulmonar es más prometedor que el del carcinoma broncogénico. La extensión debe depender de la ubicación del tumor y de la edad del enfermo.

Hay variados puntos de vista respecto del uso de la roentgenterapia. Algunos piensan que siempre debe usarse, en tanto que otros la usan sólo ante las recurrencias.

Les auteurs présentent trois malades atteints de lymphosarcoma primitif du poumon. Pour cette petite série, on pourrait croire que le pronostic du lymphosarcome pulmonaire opérable est plus favorable que celui du cancer bronchique. L'étendue de la résection doit dépendre de la localisation de la lésion et de l'âge du malade. Il y a différentes opinions concernant l'emploi de la radiothérapie. Certains pensent qu'elle devrait toujours être utilisée, tandis que d'autres la récidivantes.

ZUSAMMENFASSUNG

Beschreibung von 3 Kranken mit primärem Lymphosarcom der Lungen. Von dieser kleinen Reihe könnte man den Glauben ableiten, dass die Prognose beim resezierbaren pulmonalen Lymphosarcom besser ist als beim bronchogenen Carzinom. Das Ausmass der Resektion muss abhängig sein von der Lokalisation des Befundes und dem Alter des Kranken. Die Anschauungen über die Anwendung der Röntgentherapie sind verschieden. Von mancher Seite wird angenommen, dass sie immer zur Anwendung kommen sollte, während andere sie nur für rezidivierende Herde brauchen.

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Some Observations on the Clinical Picture and Therapy of Putrid Pulmonary Processes, Based on About 200 Cases Observed and Treated

J. SWIERENGA, M.D., F.C.C.P.*
Utrecht, Netherlands

By putrid pulmonary process is meant an inflammatory process of the lung in which one or more abscess cavities have developed. Consequently it is not an inflammation in a preformed cavity.

This comprehensive group includes both acute and chronic putrid pneumonia as described in the French literature (Sergent) as well as gangrene of the lung. These diseases may be due to a variety of causes. We have therefore subdivided them into bronchogenic and metastatic processes and processes developed via a pulmonary infarct or as a result of direct outgrowth from an adjacent organ.

1. *Putrid bronchogenic processes*

a. Processes subsequent to a pulmonary process.

Formerly these were referred to as primary pulmonary abscesses. These diseases occur particularly in degenerates, e.g. diabetics, alcoholics and elderly people, and in addition specific bacteria are much more conducive than others to the development of abscess cavities. Staphylococcus aureus haemolyticus and Friedländer's bacillus in particular have a bad record.

Patients suffering from this clinical picture are generally very ill and toxic although these processes may also be primarily chronic, i.e. the putrid pulmonary process is found rather unexpectedly during the examination without the patients having suffered serious illness previously. In this connection Sergent uses the term primary, chronic pulmonary abscess, as distinguished from the secondary, chronic pulmonary abscess following an acute clinical picture.

b. A special position is relegated to processes of diseases developed after aspiration of infected material. These abscesses used to be of frequent occurrence after the patient had been anaesthetized by ether, especially when he had not an empty stomach when operated on. Localisation of these processes depended on the position of the patient during or after the operation. Preferential locations are dorsal segment of the upper lobe and the apical segment of the lower lobe. The abscesses following tonsillectomy performed on an anaesthetized patient in half-sitting position are notorious.

In these instances the diseases are often observed in the lower regions of the lung, particularly on the right.

Lesions of this type are also frequently found in patients who vomit at regular intervals, in epileptics and in sufferers from diseases of the esophagus.

*Of the Pulmonary Diseases Department of St. Anthony's Hospital.

The aspirated foreign body which may rapidly cause serious inflammatory processes deserves special consideration.

c. Putrid processes situated behind a bronchostenosis.

Stenosis arising from a bronchiogenic carcinoma is prominent among such processes. Abscess cavities are frequently formed in the obstruction infiltrate situated on the periphery of the bronchostenosis. They are not to be confounded with cavities developing immediately in a peripheral carcinoma. The wall of the latter cavities has a much more irregular shape and often have sequestra situated in the abscess cavities.

Besides the carcinomatous stenosis, stenoses resulting from non-specific inflammatory processes and tuberculosis may be the causative factor in these abscesses.

We find in the literature that the French school of Sergent postulates that putrid processes generally develop in conjunction with a pulmonary process in which anaerobic bacilli might be a factor. Brock advocates bronchial embolism in particular, and feels that many putrid pulmonary abscesses have their origin in aspiration of infected material from the mouth or throat, for example.

The localisation of many pulmonary abscesses in particular favours Brock's theory.

2. *Metastatic pulmonary abscesses*

These generally develop in patients suffering from a serious disease who are affected by pyemia. Septic emboli may be disseminated from a suppurative focus through the arterial circulation. As a result multiple lung abscesses may develop which are not typical in their localisation. They may occur in large numbers, although in certain cases their incidence may be low. These metastatic abscesses are of rather frequent occurrence especially in puerperal infections and in infections by staphylococci.

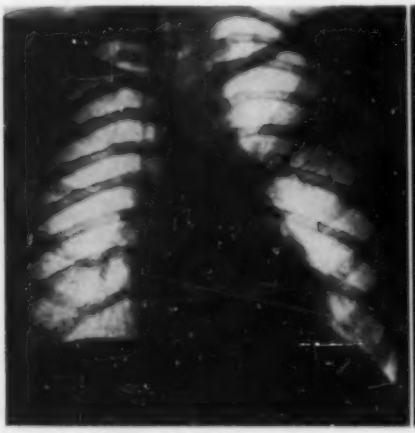

FIGURE 1

FIGURE 2

Figure 1: Métras catheter in bronchus of left upper lobe.—*Figure 2:* Catheter in apicalbronchus of left lower lobe.

3. *Putrid pulmonary processes produced by spread from an adjacent organ.*

In this class we should include, for example, abscesses by amoebae by an invasive spread from the liver.

Such processes may also be due to diseases of the esophagus or, for example, to osteomyelitis of a rib. Pulmonary abscesses are not infrequently observed when an esophagus carcinoma invades the lung, when these lesions may occur as a result of aspiration of infected material. The inflammation caused by the carcinoma may also produce a local putrid process. Putrid pneumonias have also been reported in the case of rupture of infected mediastinal cysts in the bronchial tree.

Dermoid cysts have a bad record in this respect. While anomalies of ribs may be responsible for such pulmonary lesions, the possibility of inflammation of a vertebra should also be borne in mind. We have seen a case of putrid pneumonia caused by staphylococci resulting from rupture of osteomyelitis of a vertebral body into the lung.

4. *Putrid pulmonary processes in conjunction with a pulmonary infarct.*

Some writers state that a pulmonary infarct may be secondarily infected, thereby producing a putrid process.

Other writers, e.g. Levin, Kernokan and Moersch, postulate that a pulmonary abscess generally develops secondary to an infarct due to a septic embolus. Furthermore, it is stated that there is a greater likelihood of abscesses in the case of large infarcts, inadequate circulation, poor function of surrounding pulmonary tissue and bacteria carried in the embolus or in the surrounding tissue. The foregoing summary shows that a great many causative factors may lead to a putrid process. The clinical picture, already referred to in passing, may vary greatly. In some instances acute clinical pictures are observed concomitant with high temperatures and pronounced activity phenomena.

Generally no distinct pulmonary symptom is noted during the first few days, after which large quantities of purulent sputum, sometimes foul-smelling, are suddenly expectorated. In addition there is an insidious clinical course in which the pulmonary symptoms gradually present themselves. Table I tabulates the causative factors we found in our cases.

Bronchiogenic carcinoma has been expressly omitted since in this case the primary disease is much more important than the secondary putrid pneumonia.

TABLE I

Causative factors		
Pulmonary process		121
Aspiration	tonsillectomy	8
	general anaesthesia	24
	various causative factors	22
	(e.g. foreign bodies megaesophagus)	
Bronchostenosis (except Carcinoma)		7
Pulmonary infarct		3
Metastatic		4
Periarteritis nodosa		1

The causative organisms of putrid pneumonia may be of many kinds, but Staphylococcus aureus haemolyticus, Friedländer's bacillus and Streptococcus haemolyticus are, in fact, of very frequent occurrence. Anaerobic bacteria as well as spirilla and spirochetes may also be present. The latter generally give rise to foul-smelling sputum. This type of process used to be referred to as pulmonary gangrene. X-ray examination frequently reveals very large abscess cavities in this type in particular.

In the case of putrid pulmonary processes having a chronic course there is frequently roentgenologic evidence of a dense fibrotic process in which a number of small abscess cavities are present. This is referred to in the French literature as pyosclerosis (Cocquelet). The planigraphic picture of such pyosclerosis in particular is typical. In this type of process dense lesions are encountered interspersed with multiple small cavities. Pathologically and anatomically this is also a typical picture, being in fact a lung area showing sclerotic changes and scattered small abscesses. The clinical pictures of the processes caused by bronchostenosis or a septic embolus and the like show wide divergences. Differential diagnosis reveals that the chief clinical pictures are different types of pulmonary tuberculosis, softened tumours, infected bronchial cysts, bronchiectases, fungus infections of the lung and encapsulated empyemata. It is absolutely essential that x-ray examination, i.e. taking conventional postero-anterior, lateral radiographs and planigraphic films, should be accompanied by bronchologic examination by means of bronchography and bronchoscopy.

This examination should be performed particularly with a view to rule out the possibility of bronchostenosis, since a number of putrid pneumonias are found to be due to bronchostenosis even when all other methods of examination are negative. Bronchologic examination is the only possible means of identifying such a disease and it is also of value in obtaining an idea of the nature of the lesions in the mucous membrane and the source of any pus secreted. Laboratory examination is very important. Attention

FIGURE 3: Big lung abscess in the right lower lobe, which was treated with antibiotics, during 2 months.

should be especially focussed on the sputum examination, i.e. the bacteriologic, cytologic and mycologic examination.

The therapy of pulmonary abscesses has been a serious problem for many years and many publications in the period from 1920 to 1940 report a high case fatality rate.

Allen and Blackman collected 2014 cases up to 1936, the mortality rate in this series being 34.2 per cent. Monod and Schneyder also report a high mortality rate. Shaw and Paulson find a mortality rate of 30-40 per cent in certain groups of pulmonary abscesses.

Many methods of treatment were used prior to the discovery of the modern antibiotics and chemotherapeutics.

FIG. 4

FIG. 5

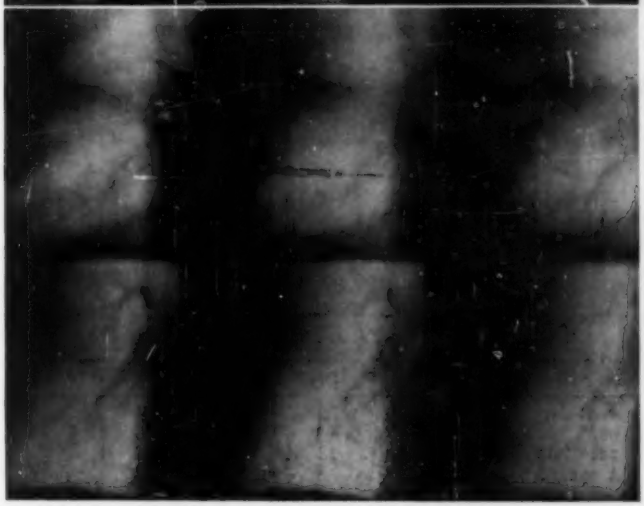

Figure 4: Planigraphy of case 3.—*Figure 5:* Planigraphy of case 3 after treatment. The abscess has disappeared.

Intravenous alcohol injections, intravenous carbon injections, sodium benzoate injections, for example, were resorted to, while many attempts were also made to use neoarsphenamine. Vaccines and sera were also tried out. While drug therapy was employed at this time, attention was also given to postural drainage. Even ultra-short wave radiation was tried.

Since collapse therapy was of value in cavernous pulmonary tuberculosis this technique has also been applied to pulmonary abscess.

Various publications reported the therapeutic results obtained with intra- and extrapleural pneumothorax, thoracoplasty and exeresis of the phrenic nerve.

All these publications showed that this therapy was ineffectual in the treatment of putrid pneumonia. A more effectual surgical treatment is the technique of open drainage advocated in particular by Neuhof and Touroff in the U.S.A., by Santy and Bérard, Monod and Iselin in France, and by Zaayer in the Netherlands.

The operation may be performed in one or two stages and usually yields satisfactory results in the case of abscesses which are solitary and thin-walled.

Touroff reports 70-80 per cent recoveries. Monod finds 52.8 per cent recoveries as against a poor result of 31.1 per cent, the unimproved cases being 16 per cent.

Although this technique represents an advance, putrid pneumonia remained a serious clinical picture showing a high mortality rate, with many patients not recovering.

In several cases in which this therapy was applied a fistula developed with an external opening regularly discharging secretion. There was often a communication from the bronchial tree to the exterior of the body. In some instances this may be unpleasant to the patient, there being every possibility of an infection from the exterior. In other cases there remained epithelialized abscess residuals or extensive bronchiectatic lesions still continued to be present in the neighbourhood of the abscess. For obvious reasons the complaints of these patients persisted. In the cases we treated before the advent of antibiotics the mortality rate was 40 per cent, there being no recovery in 33 per cent (Table II).

After the discovery of sulfonamides and subsequently of the modern antibiotics such as penicillin, steptomycin and the tetracyclines, these agents were immediately used to treat putrid pulmonary processes.

The percentage of recoveries by internal therapy alone was thereby increased, but it was nevertheless impossible for many cases to be cured completely.

TABLE II

Number	37	Deaths
operated	22	11
drainage	10	5
resection	12	6
not operated	13	4
total		15 (40 per cent)
not cured	12	(33 per cent)
cured	10	(27 per cent)

Attempts were made to apply aerosol therapy. Some writers report good results, but in our opinion it serves no useful purpose in pulmonary processes of this type since it is the diseased area in particular which shows poor ventilation, so that the medicine introduced by means of the aerosol does not, in fact, arrive at the site of the disease.

Even before the application of antibiotics on a larger scale many attempts were made to obtain more effectual treatment by means of excisional therapy. In view of the frequently high toxicity and the great secretion of pus the mortality rate was high. The great secretion of pus created a risk of contra-lateral disseminations. These disseminations were conducive to the development of new abscesses via the bronchial route, thereby increasing the case fatality rate. There was also danger of hemorrhages especially in still active putrid processes. The chances of hemorrhages during or after the operation are greater than, for example in excisional therapy applied to bronchiectasis. The literature by Monod, Schneyder, Kent, Ashburn and Cory, for example, show that these writers also had a high operative mortality rate.

Better results were obtained by excisional therapy after the patients had been pretreated with general antibiotic agents. However, the publications of, for instance, Valle, Sweet, Neerken and Grow and Cory, reveal that the mortality rate still remains high after this pretreatment. Their case mortality rate varies from 10 to 25 per cent. Subsequent statistics on cases where the antibiotic therapy was continued for a longer period show still better results (Chaptal, Campo and Germain, Fox, Hughes, Sutliff).

Besides general and surgical treatments of pulmonary abscess, local therapy of the abscess with the use of proper drainage in conjunction with local antibiotic therapy has been attempted on several occasions. Lemoine and Rose reported fairly satisfactory results with bronchoscopic therapy in putrid pneumonias. The pus is evacuated from the draining lobe bronchus by means of a catheter and the mucous membrane is subsequently treated with adrenalin. They do not specifically mention the necessity of

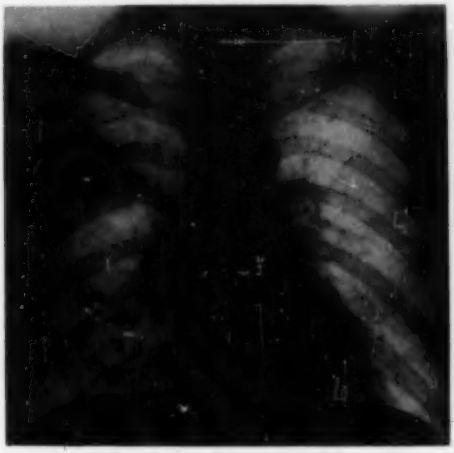

FIGURE 6: Big lung abscess in right upper lobe.

prolonged antibiotic therapy. Samson also advocates bronchoscopic treatment. He attributes the effectiveness of bronchoscopy to various factors, for example evacuation of the secretions, eliciting an irritating cough, dabbing the edematous wall and aspiration of pus from the abscess by means of a long rubber tube. We have no actual experience with this procedure.

Monaldi suggests the technique of draining the abscess by means of a thin rubber drainage tube, as he recommended in tuberculous cavities, and claims good results.

Transparietal punctures also led to amelioration or recovery in some cases. In this method the abscess is punctured whereupon the pus is drained, penicillin being instilled locally. Trocmé, Dupont et al., Drouet and Faivu et al. report having obtained fairly satisfactory results by this procedure.

FIG. 7

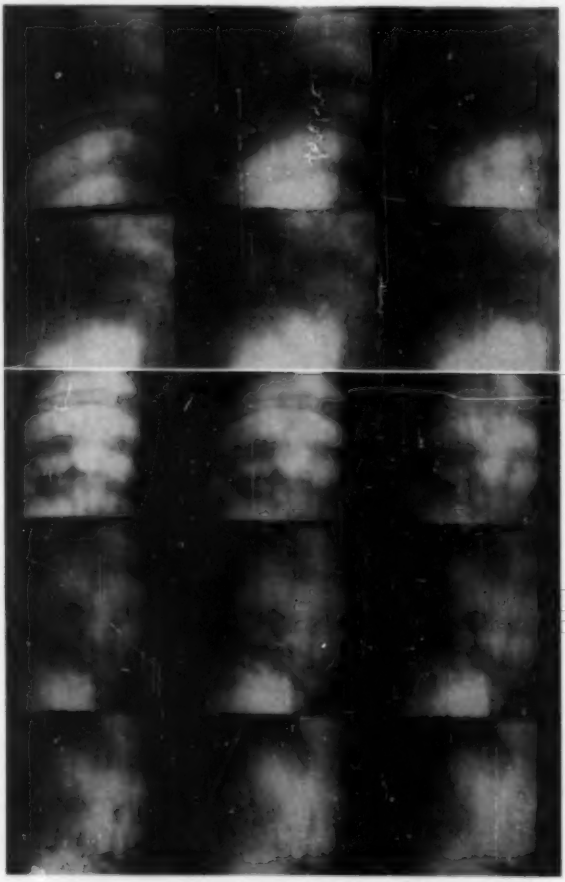

FIG. 8

Figure 7: Planigraphy of case 6 with cavity in pneumonic infiltrations.—*Figure 8:* Planigraphy of same patient as picture 7. It is evident, that there is an important infiltration. Here was done a segmental resection of the dorsal segment of the right upper lobe.

A very effectual method of local treatment is the one first applied by the Mattei school at Marseilles, enabling catheterization of the draining bronchus of the abscess by means of an ingenious type of sound designed by Henri Métras.

Mattei and co-workers reported having obtained favourable results by this method in which on the one hand the pus was drained and on the other antibiotics were instilled locally.

Métras, Charpin and Gregoire found a rate of cure of 72.5 per cent while in other cases the clinical picture often showed considerable amelioration. Admittedly thin-walled residual cavities are fairly frequently observed after the treatment. Many writers are of the opinion that these residual cavities are of little clinical importance (Charpin, Métras, R. Kourilsky and G. Decroix, Trocmé and Carré, Mannes). Since 1947 we have applied the combined general antibiotic therapy in conjunction with the local antibiotic therapy in all putrid pulmonary processes.

The antibiotics used are determined by the respiratory flora present. Catheterizations with the Métras Sound are a daily occurrence. The technique of this treatment is not difficult. It is as follows: Half an hour before treatment we give the patients 100 mgr. of luminal and 5 mgr. dicodid. The treatment is started with local anesthesia of larynx, pharynx, trachea and main bronchi with pantocaine ½ per cent. When this local anesthesia is complied the catheter can be introduced very easy with the aid of the laryngeal mirror. When the catheter has been placed in the trachea, it is necessary to scope the patient under fluoroscopic control. The catheter can be placed in the segmental bronchus of the abscess. It is possible to catheterize any segmental bronchus, because it is possible to get catheters with ends, curved at various angles. When the catheter is correctly placed, we try to aspirate pus. After aspiration antibiotics are instilled in 5 cc physiologic saline solution (Figs. 1 and 2).

Generally 200,000 units of penicillin and ½ gram of streptomycin is given in each treatment. The results obtained by this treatment have been favourable. Our total number of patients treated by this method was 119, 67 of whom were cured by the sole application of the combined general and local treatment.

In view of the fact that lesions were incompletely cured, this treatment was followed by excisional therapy in the case of 52 patients.

When this technique was in its early stages we felt anxious about a

TABLE III

		Deaths		No.	Per Cent	Per Cent
Total	155	5	Cured	150 =	96.8	
General treatment	20	3	Cured	17 =	85	89
General treatment + excisional therapy	16	1	Cured	15 =	94	
General treatment + Métras	67		Cured	67 =	100	99
General treatment + Métras, excisional therapy	52	1	Cured	51 =	98	

FIGURE 9

FIGURE 10

Figure 9: Thinwalled cavity after general and local treatment with antibiotics. A cavity rest like this is on the moment no indication for operation.—*Figure 10:* Planigraphy of the same case as 9.

relapse so at that time it is possible too many patients may have been subjected to excisional therapy. There was one operative death in these 52 patients.

Furthermore, we have treated several cases with antibiotics with or without the application of excisional therapy, local treatment being omitted, however. The total number of patients in this group was 36 of whom 32 were cured (Figs. 3-10).

In any case the combined local and general treatment ensured that, if an operation became necessary, it could be confined to a small resection which was performed as a segmental resection. It is evident from the foregoing that after the introduction of the combined local and general antibiotic therapy, as a result of the use of the Métras catheter the once dangerous putrid pneumonia has come to be a disease curable in virtually 100 per cent of the cases. It is also clear that drainage no longer serves any useful purpose.

SUMMARY

The results are reported of the treatment of 192 cases of putrid pneumonia performed in the Pulmonary Diseases Department of St. Anthony's Hospital, Utrecht. A marked difference is observed after the introduction of the combined general and local antibiotic therapy in conjunction with the Métrus Catheter.

This therapy enabled successful results to be obtained in virtually 100 per cent of the cases. In our cases the percentage of patients who are still subjected to an operation is 40 per cent.

In recent years the number of operations has been on the decrease since small residuals persisting after the treatment have found to be of no clinical importance. It is postulated that the above technique is the treatment of choice for all putrid pneumonias, thereby ensuring the best possible results.

Acknowledgment: All the operations were performed by Dr. M. C. A. Klinkenbergh, Dr. A. Schaepkens van Riempst and co-workers, the anaesthetist being Dr. H. de Zwaan.

RESUMEN

Se relatan los resultados del tratamiento de 192 enfermos de neumonía pútrida, en el departmento de enfermedades pulmonares del Hospital de San Antonio de Utrecht. Se nota una marcada diferencia después de la introducción del método de combinación general de antibióticos en conjunción con el cateter de Metras.

Este tratamiento permitió resultados satisfactorios en el cien por ciento de los casos virtualmente. En nuestro grupo, el porcentaje de enfermos que aún se han sujetado a operaciones es de 40 por ciento.

En años recientes el número de operaciones ha decrecido puesto que los residuos pequeños que persisten después del tratamiento se ha encontrado que no tienen importancia clínica.

Se sostiene que la técnica antes descrita, es el tratamiento de elección para todas las neumonías pútridas, asegurando con ella los mejores resultados.

RESUME

L'auteur rapporte les résultats du traitement de 192 cas de pneumonie putride suivis dans le Service des Affections Pulmonaires de l'Hôpital St.-Antoine à Utrecht. On note une nette différence après l'utilisation du traitement antibiotique à la fois général et local associé à l'usage de la sonde de Metras.

Ce traitement permit d'obtenir des résultats satisfaisants dans virtuellement 100% des cas. Dans notre groupe, le pourcentage des malades qui sont encore soumis à une opération est de 40%.

Dans ces dernières années, le nombre des opérations a été en diminution malgré un petit nombre de reliquats persistants après le traitement, qui sont sans importance clinique. Il est admis que la technique ci-dessus est le traitement de choix pour toutes les pneumonies putrides, assurant pour la suite les meilleurs résultats possibles.

ZUSAMMENFASSUNG

Es werden die Ergebnisse vorgelegt über die Behandlung von 192 Fällen von eitriger Pneumonie, die in der Abteilung für Lungenkrankheiten des St. Anthony Hospitals, Utrecht, gewonnen wurden. Eine deutliche Differenz wurde beobachtet nach der Einführung der kombinierten allgemeinen und lokalen antibiotischen Therapie in Verbindung mit dem Metraskatheter.

Diese Therapie ermöglichte es, dass erfolgreiche Ergebnisse in wirklich 100% der Fälle erlangt wurden. In unserer Gruppe beträgt der Prozentsatz von Patienten, die noch einer Operation unterzogen werden müssen 40%.

In den letzten Jahren ist die Zahl der Operationen zurückgegangen nach dem sich herausgestellt hatte, dass kleine Reste, die nach der Behandlung bestehen blieben, ohne klinische Bedeutung waren. Es wird die Forderung aufgestellt, dass die oben dargestellte Technik die Behandlung der Wahl für alle eitrigen Pneumonien wird, da auf diese Weise die bestmöglichen Ergebnisse erzielt werden.

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The Role of the Cycloserine (Seromycin) Blood Level in the Treatment of Pulmonary Tuberculosis and the Prevention and Control of Cycloserine (Seromycin) Toxicity*

C. X. HOLMES, M.D., GEORGE E. MARTIN, M.D., F.C.C.P.
and K. F. FETTERHOFF, M.D., F.C.C.P.
Pittsburgh, Pennsylvania

Introduction

The cycloserine serum level was used as the control in a study of 60 treatment failure cases of pulmonary tuberculosis. It was determined that those cases that maintained a cycloserine serum level between 20 and 40 micrograms per milliliter of serum showed both radiographic and bacteriologic response uncomplicated by cycloserine toxicity.

The method used in determining the cycloserine serum level at the Pittsburgh State Tuberculosis Hospital was a modification of the Jones Method of Colorimetric Determination of the cycloserine in the serum.

Treatment and Results

Sixty treatment failure cases between the ages of 15 and 60 years; the average, 41 years of age, were studied for nine months. The first 10 cases chosen were our pilot cases in which all the usual laboratory tests were obtained and, in addition, through the cooperation of the Leech Farm Veterans Administration Hospital in Pittsburgh, pretreatment and a post 90 day treatment period electroencephalograms and complete neurological examinations were given each patient. All tests were negative and these patients were given cycloserine in divided doses that kept the cycloserine serum level below the 40 microgram level, the safe upper serum level as determined by Epstein[1] in his original work with cycloserine.

The average dose of cycloserine administered in this study was 14 milligrams per kilogram of body weight, given in divided doses, morning and evening. This dose is somewhat higher than the average dose noted by Epstein[2] in a more recent report in which he found the average dose used in untreated cases of cycloserine and INAH was 10 milligrams per kilo.

It is significant that our study revealed that there was no correlation of body weight and the dose of cycloserine an individual patient might require as determined by the cycloserine serum level. This dose ranged from 0.25 gms. to 1.5 gms. daily. In addition to the routine laboratory tests, a chest x-ray film and bacterial examination of sputum by smear and culture were made monthly.

After three months of treatment with cycloserine alone, INAH was added in the dose of 3 milligrams per kilo of body weight, also given in divided doses morning and evening; and the two drugs were continued in combination for the remaining six months of the study.

*Pittsburgh State Tuberculosis Hospital, Division of Tuberculosis Control, Pennsylvania Department of Public Health.
Cycloserine for this study was supplied by Eli Lilly Company as Seromycin.

The cases chosen had been hospitalized from one and one-half to seven years, average four years, and had shown no significant response to any of the antimicrobial drugs either by x-ray film or sputum examination.

There was one case in the pilot group who, though considered a pre-psychotic, was treated because of the negative electro-encephalogram and neurological findings.

All patients were given 0.5 gm. of cycloserine initially and after one week of medication the cycloserine serum level was obtained and the drug dose adjusted to keep the serum level below 40 micrograms.

Two patients showed psychiatric reactions; after four months of treatment in the pre-psychotic and after five months in the other patient who showed this type of toxicity. In each case the cycloserine serum level elevated abruptly above 50. The cycloserine was discontinued immediately, the serum level fell to zero in 36 hours, and in the non pre-psychotic the psychiatric symptoms persisted. Two other patients showed early neurotoxic symptoms of tremor, weakness and mild disorientation. The serum level at the onset of these symptoms was found to be above 40.

However those patients who remained in the 20-40 range of serum level gave no evidence of any cycloserine neuropsychiatric toxicity.

After nine months of cycloserine therapy, six months of INAH therapy combined, we found that 25 per cent of this treatment failure group had negative sputa by concentration and culture and 42 per cent of the cases showed moderate to marked regression of the x-ray shadow casting lesion.

SUMMARY

Cycloserine alone was administered during the first three months of a study of 60 treatment failure cases of pulmonary tuberculosis. For the remaining six months of the study, cycloserine was combined with isoniazid.

The Jones Modification of the colorimetric determination of cycloserine in the serum was employed in determining cycloserine blood levels. The control and effective treatment levels ranged between 20 and 40 micrograms of cycloserine per mililiter of blood.

Six per cent of the cases studied showed neurotoxicity. However, these toxic effects were reversible without sequelae when cycloserine was discontinued.

There was sputum conversion in 25 per cent and regression of x-ray lesions in 42 per cent of the cases studied.

It was concluded that with cycloserine blood level determinations, cycloserine toxicity can be prevented or controlled; and that cycloserine is an effective antimicrobial drug, best used in combination with isoniazid.

RESUMEN

Se administró cicloserina sola durante los primeros seis meses de estudio en 60 casos en que el tratamiento había fracasado para la tuberculosis pulmonar. Durante los seis meses siguientes, se administró la cicloserina asociada a la isoniacida.

Se empleó la modificación de Jones para la determinación colorimétrica de la cicloserina en el suero de la sangre.

El control y los niveles de tratamiento efectivo oscilaron entre 20 y 30 microgramos de cicloserina por mililitro de sangre.

En seis por ciento de los casos se presentó neurotoxicidad. Sin embargo, estos efectos tóxicos, fueron reversibles y sin secuelas al suspenderse la cicloserina.

Hubo conversión de los esputos en 25 por ciento y retroceso de lesiones a los rayos X en 42 por ciento.

Se incluye que las determinaciones de los tenores de cicloserina en la sangre, permiten controlar o prevenir la neutrotoxicidad y que la cicloserina es una droga antimicrobiana efectiva, siendo mejor combinada con isoniacida.

RESUME

La cyclosérine fut administrée seule pendant les trois premiers mois pour étudier son action sur 60 malades qui constituaient des échecs thérapeutiques de tuberculose pulmonaire. Pour les six autres mois de l'étude, la cyclosérine fut associée à l'isoniazide.

La modification de Jones pour la détermination colorimétrique de la cyclosérine dans le sérum fut utilisée pour évaluer les taux sanguins de cyclosérine. Les taux de contrôle et d'efficacité thérapeutique atteignirent entre 20 et 40 microgrammes de cyclosérine par millilitre de sang.

5% des cas étudiés montrèrent une neurotoxicité. Cependant ces effets toxiques disparurent sans séquelles, lorsque la cyclosérine fut interrompue.

Il y eut la négativation de l'expectoration dans 25% des cas étudiés, et une régression des lésions radiologiques dans 42%.

L'auteur conclut qu'avec la mesure de la concentration sanguine de cyclosérine, la toxicité de ce produit peut être évitée ou contrôlée; et que la cyclosérine est un produit antimicrobien efficace, dont l'utilisation est plus valable en association avec l'isoniazide.

ZUSAMMENFASSUNG

Cykloserin allein wurde zur Anwendung gebracht während der ersten drei Monate in einer Beobachtungsreihe von 60 Behandlungs-Versagern bei Lungentuberkulose. Während der übrigen 6 Monate der Untersuchung wurde Cykloserin kombiniert mit INH.

Es wurde die Jones-Modifikation der colorimetrischen Cykloserin-bestimmung im Serum benutzt bei der Bestimmung der Cykloserin-Blut-Spiegelwerte. Die Kontrollwerte und die wirksamen Behandlungswerte schwankten zwischen 20 und 40 mg Cykloserin pro Kubikzentimeter Blut.

6% der beobachteten Fälle wiesen neurotoxische Symptome auf. Jedoch liessen sich diese toxischen Effekte beheben ohne weitere Folgen, wenn mit dem Cykloserin aufgehört wurde.

Es ergaben sich Sputum-Konversionen von 25% und Rückgang der Röntgenbefunde bei 42% der beobachteten Fälle.

Es wird gefolgert, dass man mit Cykloserin-Blutspigel-Bestimmungen eine Cykloserin-Toxizität verhindern oder beherrschen kann.—Das Cykloserin ist eine wirksame antimikrobielle Substanz, die man am besten in Kombination mit INH benutzt.

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Evaluation of Lipoid Pneumonia

R. H. SUNDBERG, M.D., F.C.C.P., KARL E. KIRSCHNER,* M.D.
and MAURICE J. BROWN, M.D.
San Diego, California

Granulomas of the lung due to lipoid substances have been recognized for many years. Formerly these were considered to be secondary to the aspiration of mineral, vegetable, or animal oils. Pinkerton's[1, 2] classical studies demonstrated that these oils, when introduced into animals, elicited inflammatory reactions of the lung which varied from mild hyperemia to severe necrotizing pneumonitis.

The term lipoid pneumonia has been given frequently to the pulmonary inflammation and fibrosis produced by inadvertent aspiration of inorganic or organic fatty materials. However, it has become apparent in recent years that many patients with so called oil granulomas give no history of aspirating or using any type of oil, and a great number of the granulomas themselves reveal no demonstrable oil deposit on chemical analysis. Many of these granulomas, however, show deposits of cholesterol that are of endogenous origin. From these findings, two separate groups of lipoid granulomas can be said to emerge—both entirely different in etiology and pathogenesis. Their only common characteristic is the presence of substances which are soluble in fat solvents.

In this study, lipoid pneumonias are classified as (1) exogenous, manifested by paraffinomas or oil granulomas due to aspiration of mineral oil, vegetable oil, or animal oil; and (2) endogenous (cholesterol pneumonitis, Wegener's granulomas, etc.) resulting from metabolic, allergic, neoplastic, inflammatory, embolic, or toxic reactions within the lung tissue.

TABLE I—ORIGIN OF CHOLESTEROL DEPOSITS IN PULMONARY PARENCHYMA

A. Local conditions:	B. Systemic conditions:
Mobilization of alveolar lining cells, and transformation into lipophages in: a) pulmonary congestion, b) pulmonary inflammation, c) around neoplasms, d) around parasites, fungi or pollens, e) around foreign bodies, f) around infarctions, g) pulmonary alveolar proteinosis.	Deposition of lipoid laden histiocytes from the reticuloendothelium in: a) Congenital diseases: Hand-Schuller-Christian disease, primary Xanthomatosis. b) Metabolic diseases: Secondary Xanthomatosis, Diabetes Mellitus, Myxedema, lipoid nephrosis, large cell hyperplasia of Schulze. c) Allergic diseases: Loeffler's granulomas, Wegener's granulomatosis. d) Circulatory diseases: Pulmonary infarctions, fat embolisms, periarteritis. e) Inflammatory diseases: Organizing pneumonitis, bronchiectasis, abscesses. f) Degenerative diseases: Atheromatosis, Xanthomatous degeneration of tumors.

*Department of Pathology, Mercy Hospital. Now at San Luis Obispo, California.

Exogenous lipoid pneumonia, the first classification, is usually induced by the dropping or spraying of plain or medicated oil into the nose for therapeutic purposes. This may cause aspiration of the oil into the tracheobronchial tree. The American Medical Association Council on Pharmacy and Chemistry,[3] in 1942, warned against the indiscriminate use of mineral oil, since it could, if taken orally, particularly before sleep, be aspirated or regurgitated from the stomach into the tracheobronchial tree. This has been proved by giving iodized oil by mouth to persons about to retire. X-ray examination demonstrated that some of the oil appears in the lungs. Cod liver oil forceably administered to infants, especially when crying occurs, also may cause quantities of the oil to be aspirated. Lipoid pneumonia has been discovered at autopsy in children who died following prolonged, debilitating illnesses. It is possible that some milk fats may have been responsible for pneumonitis in a few of the cases. Older people, in particular those who are weakened by prolonged illness, also may develop oil pneumonitis of dietary origin.

When iodized vegetable oils are introduced into the tracheobronchial passage for diagnostic purposes, they can produce a temporary, mild, inflammatory response. Because of this some surgeons prefer to postpone operations after bronchograms are done, until most of the administered oil has been expectorated. Small quantities of iodized oil may be retained in the lung for long periods and produce no lasting inflammatory reactions.

The second, or endogenous, classification of lipoid pneumonias is also referred to as cholesterol pneumonitis, a term adopted by Robbins and Sniffen[4] and used to designate a pulmonary condition characterized by chronic inflammatory changes and excessive deposits of cholesterol in the tissues. According to McDonald and Hogdson[5] cholesterol pneumonia is the commonest form in which lipid is encountered in the lung.

Roentgenograms may reveal oil pneumonitis of the exogenous or endogenous type in persons who are apparently healthy. The symptoms may include mild fever, chest pain, and coughing. The size of the lesion is often startling and may cause the physician to suspect chest tumor. Clinical diagnosis of lipoid pneumonia is extremely difficult and is often tentative, based on the patient's testimony. The patient rarely ever volunteers evidence for the cause so the physician must seek clues by direct questions. Diagnosis may be made tentatively if the history is positive. The presence of oil droplets in the sputum, located either intracellularly or extracellularly, is strongly suggestive of oil granuloma. Failure to find droplets, however, does not exclude the diagnosis. If previous x-ray films of the chest indicate that a density has been of long duration, the physician will feel more secure in his diagnosis than if no prior information is available. Biopsy of the lung is the most dependable diagnostic procedure.

When the history and pulmonary roentgenographic findings suggest lipoid pneumonia diagnostic studies should include examination of 24-hour sputum specimens collected daily for three to five days. The patient is placed on a strict, fat-free diet for four days prior to the period of collection. A drop of sputum is deposited with a platinum loop on each of four glass slides. A drop of saline is added to establish a thin spread.

The sputum is centrifuged for five minutes and the sediment is spread on a glass slide in a similar manner. Slides are dried in the incubator. Two of the slides are stained with Sudan IV and two with Wright's stain modified by Little.[6] Sputum is considered positive for lipoid pneumonia when the Wright stain shows the characteristic macrophages which contain clusters of vacuoles, when the vacuoles stain orange-brown with Sudan IV, or if abundant extracellular fat-staining material is present.

Roentgenologically, two main types of lipoid pneumonia can be distinguished—(1) a circumscribed involvement within a lobe which can be mistaken easily for a tumor; and (2) a diffuse type which usually affects one or more lobes and is the more common of the two. During the acute phase, lipoid pneumonia gives rise to a soft density within one or more lobes of the lung which cannot be differentiated from any form of pneumonitis. Oil aspiration pneumonia has a predilection for the right middle and right lower lobes. The upper lobes are primarily affected in bedridden patients or infants. Since lipoid pneumonia frequently undergoes fibrosis, it can cause a contraction of the involved area. Surrounding lung tissue then appears emphysematous. This fibrosis and contraction are responsible for the characteristic "ground glass" appearance. This is the best known x-ray film feature of lipoid pneumonia and represents the late phase of the disease.

In the majority of cases of oil pneumonitis, no treatment is indicated except that intake of exogenous oil must be eliminated. When there is a large lesion present pulmonary resection is often employed because of difficulty in diagnosis and the possibility of bronchogenic carcinoma. localized tumor-like masses should be resected if the surgical risk seems reasonable and pulmonary function is adequate.

Most authors feel that the massive deposits of cholesterol and fibrosis described in lipoid pneumonia indicate the presence locally of some unusual metabolic factor. Also, a state of hypersensitivity may result in the fibrotic and granulomatous reaction to the foreign substance. Fienberg[7] stated that the pulmonary findings in Wegener's syndrome and those of idiopathic lipoid pneumonic granulomatosis and angiitis are similar histologically to chronic pneumonitis of the cholesterol type. Incidentally, one of our cases suggested necrotizing angiitis but was not included as it occurred in an autopsy case. By Fienberg's definition, idiopneumonic granulomatosis and angiitis refer to isolated pulmonary lesions, as differentiated from necrotizing granulomatosis and angiitis in which lung lesions are accompanied by involvement of other organs. Cholesterol pneumonitis has been called foam cell pneumonia by Chiari, according to Robbins and Sniffen.[4] This condition is characterized histologically by the prominence of intra-alveolar and interstitial foam cells as well as marked septal fibrosis.

Reaction of the lung to foreign substances depends upon two factors—the nature of the agent and the anatomical condition of the parenchyma. The number and size of the particles of the offending matter, the nature of their solvents, the time of action, and the chemical composition may combine in various ways to produce a certain reaction unit. This is opposed by the functional state of the respiratory tissue to produce a certain reaction product. The anatomical state also determines to what extent

the alien matter can be dealt with. The classical response to injury is inflammation and its aim is elimination of the injurious agent. If this cannot be accomplished, the process enters the subacute and chronic state and is specifically modified by the offending substance. The foreign body granuloma is the result. The smaller the particle, the larger the extension of the process. The process may be diffuse in the case of irritating gases, focal around silicotic particles, or wedge-shaped around foreign bodies or liquids of high surface tension, such as oils. The pathological state thus initiated is named after the foreign substance. Many have been grouped under the title of pneumoconiosis, such as anthracosis, siderosis, berylliosis, etc. Others have been included in aspiration pneumonias, specific granulomas, and infarcts.

Pathogenesis. Introduction of oil or cholesterol through the bronchial vascular tree will excite dilation and immigration of large numbers of macrophages. If the tissue is healthy, additional macrophages will be produced by metaplasia from the alveolar lining cells, all of which will engulf the substance and transport it along the peribronchial lymphatics to the bronchial lymph nodes. If the tissue has been injured previously, however, elimination will be incomplete and stagnant pools of lipoids or lipoid-laden wandering cells will form. The latter process will also take place if the amount of lipoid is disproportionately large or if the lipoid is an acute irritant. In the instance of animal and vegetable fat, some decomposition occurs and the liberated fatty acids are carried off by the blood or are combined with base to form mineral deposits. Aromatic and aliphatic hydrocarbons, on the other hand, remain as inert masses in the tissues, unless they gain access to a bronchus and can be partially expectorated. Cholesterol is almost exclusively taken up by wandering cells which are subsequently recognizable as foam cells lying in the alveolar spaces. Sooner or later, other products of the inflammation will appear, such as lymphocytes, eosinophils, and plasma cells. The deposits, by virtue of their volume and irritant nature, cause transformation of fixed reticulum cells to epithelial and foreign-body giant cells. Finally fibroblasts appear on the periphery. These wall off and organize the lesion by formation of scar tissue.

Morphology. The gross appearance of the lesions in endogenous or exogenous lipoid pneumonia is essentially the same. A slight yellowish hue is a prominent color change in the red-brown lung tissue. The lesion is prominent above the cut surface and shows increased consistency. As a rule, it is fairly well demarcated and shows round, scalloped borders. Its size varies from one inch to that of a whole lobe. The adjacent lung tissue may show minor changes, such as compression atelectasis, or severe alterations, such as fibrosis, kinking of the bronchi, and bronchiectasis with secondary inflammatory destruction.

Microscopically, both types of granulomas may look alike to the casual observer. The lesion appears as an area of organizing pneumonitis, containing many desquamated alveolar lining cells, inflammatory cells, and collagenous cells, and sometimes fat vacuoles of various sizes. Alveolar septal fibrosis, obliteration of pulmonary capillaries, and an overgrowth of marginal connective tissue containing many well developed lymph follicles are present. In addition, there is foreign body reaction in the adjacent tissue.

The histological criterion for differentiation of the two entities, endogenous and exogenous lipoid pneumonia, is marked, however, and enables the observer to name the responsible agent correctly without tissue analysis. In the cases of oils or paraffins, the macrophages present a honeycombed, vacuolated cytoplasm, which on special stain reveals large fat droplets. These cells lie within dilated air spaces in clusters or confluent masses which form pools of oil walled off by giant cells. If cholesterol is present, the macrophages show a granular, foamy cytoplasm. Special stains show fine punctate fat droplets within the cytoplasm. The typical cholesterol clefts, as seen in the vascular intima or deposits around the synovial tissue, are not apparent. Sometimes they are found in small aggregates in dilated air sacs and have an almost organoid appearance similar to adrenal cortex or xanthomatous tumors. The foreign body response is less marked but is present.

If tissue blocks are dehydrated, pulverized, and extracted chemically, the histological impression can be substantiated. In this series of nine cases, analyses were performed on those where tissue was still available. Three cases showed cholesterol content many times above the normal tissue concentration. These were classified as cholesterol pneumonitis on the basis of microscopic examination and clinical evaluation. Histochemically, the Schultz reaction for cholesterol was positive. The tissue in one case of oil aspiration pneumonitis was extracted and revealed the presence of mineral oil at melting point 17.50. In this series, nine cases of lipoid granuloma were treated surgically at Mercy Hospital over the past ten years. Originally, all of them were classified histologically as oil granulomas or paraffinomas. Study of the material, however, showed that five of them met the histological qualification for endogenous lipoid pneumonia, in accordance with clinical impression.

Etiology. The source of exogenous lipids is obvious and has been discussed above. The cause of the cholesterol deposits is much more difficult to evaluate. Under normal conditions, the body is able to absorb large quantities of cholesterol suspended in plasma or in liver, spleen,

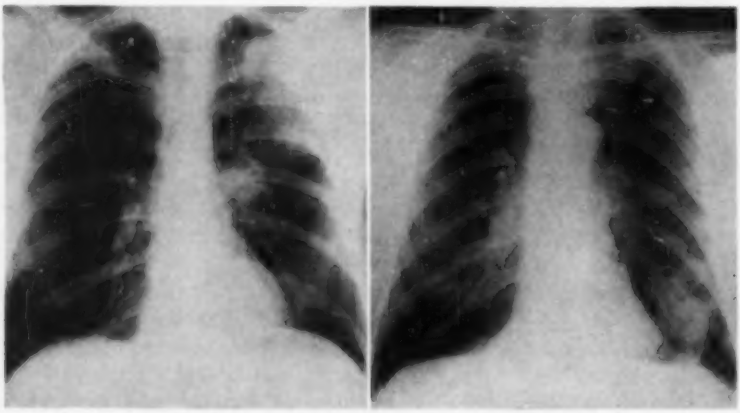

FIGURE 1 FIGURE 2

Figure 1: Example of upper lobe exogenous lipoid pneumonia (paraffinoma).—*Figure 2:* Example of lower lobe exogenous lipoid pneumonia (paraffinoma).

and lung. Sudden increases of cholesterol levels, such as injections of these substances into the blood streams of experimental animals by Hirsch and his group[8] have led to the development of cholesterol granulomas in the lung. Spontaneous fat emboli to the lung in diabetes have been described radiologically, but no pathological details are available, since the lesions underwent spontaneous absorption.

Fienberg[7] suggests that in rare cases hypersensitivity may play a role. At times large amounts of cholesterol are liberated in autolytic infiltrates such as resolving pneumonias. Cholesterol may remain in the tissue if conditions for its transport are unfavorable.[9] One of the cases in this study—cholesterol granuloma—coexisted with epidermoid carcinoma in the same lung. This may demonstrate response to autolytic tissue, as mentioned above. It seems likely that many cholesterol granulomas are absorbed spontaneously and only those lesions persist that have met with severe desmoplastic reaction.

Summary of cases. The material used for this study was obtained from Mercy Hospital records on 13 patients with the diagnosis of lipoid pneumonia. Figures 1-4. This was diagnosed clinically in four of the cases. The diagnostic basis was a history of long use of mineral oil, either in nose drops or for treatment of constipation. Oil droplets were found in the sputum in three of the four patients to substantiate the clinical diagnosis. Serial x-ray films over a 12-year period have revealed practically no change in the lesions present. No oil has been used in these patients during the past 10 years, since a tentative diagnosis was made following investigation and clinical care of them.

Nine patients were treated by thoracotomy (lobectomy or pneumonectomy). In two, oil granuloma was suspected, but because of cytological studies a question of malignancy arose. In all nine cases, a pathological diagnosis of lipoid pneumonia was made. Following the present study, a more specific diagnosis of lipoid pneumonia of endogenous origin or

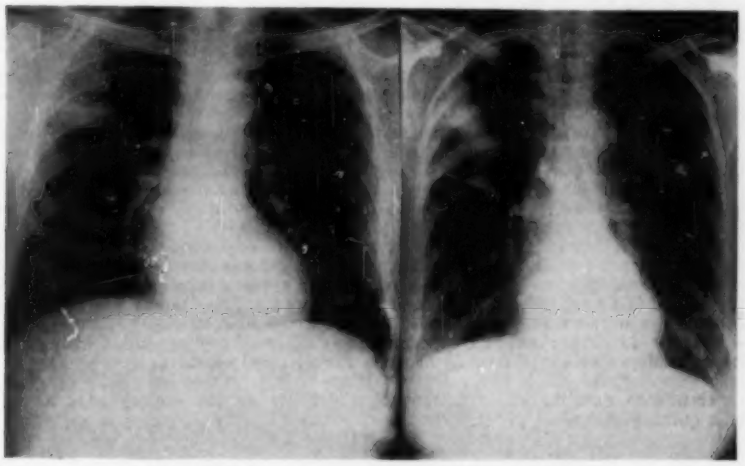

FIGURE 3 FIGURE 4

Figure 3: Example of endogenous lipoid or cholesterol pneumonitis.—*Figure 4:* Example of upper lobe endogenous lipoid pneumonia (cholesterol pneumonitis).

cholesterol pneumonitis was made in five of the cases. In four others, the classification of lipoid pneumonia or paraffinoma secondary to use of mineral oil was substantiated.

In 10 of the 13 cases, coughing and wheezing, usually nocturnal, were the prominent symptoms. These were not as severe as in the usual type of asthma and were relatively mild. In three cases, there was some chest pain. All patients coughed and raised a small amount of mucus each morning which varied in color from white to gray or light yellow. All reported that they incurred chest colds easily and that rest, customary antispasmodics, and antibiotic therapy, did not prevent the infections from being prolonged and difficult to treat. One was found to have carcinoma of the bronchus in addition to cholesterol pneumonitis of the right upper lobe. This patient lived one year following surgery. One who was operated upon eight years ago at the age of 57 died last year from myocardial infarction. The remaining 13 are living and reasonably asymptomatic. The four who did not have thoracotomy and who had diagnoses of lipoid pneumonia clinically are all living and, aside from some chest symptoms, are in fairly good health.

SUMMARY

In this study lipoid pneumonias are classified as (1) exogenous, manifested by paraffinomas or oil granulomas due to aspiration of mineral, vegetable, or animal oils; and (2) endogenous (cholesterol pneumonitis, Wegener's granuloma, etc.).

Nine cases of lipoid granuloma treated surgically in the past 10 years were reviewed in the light of new etiological factors. All had been previously classified as oil granulomas or paraffinomas. Indeed, the gross appearance of the lesions in both types may look alike to the casual observer. However, histological studies revealed that five of our cases should be classified as endogenous, rather than exogenous, lipoid pneumonia.

The source of exogenous lipids is obvious; the cause of cholesterol deposits is harder to evaluate and possible reasons for the presence of cholesterol are discussed. It seems likely that many cholesterol granulomas are absorbed spontaneously and only those lesions persist that have met with severe desmoplastic reaction. These may require thorocotomy if extensive cavitation occurs.

Those lesions of an exogenous nature may be diagnosed by repeated sputum analyses and special stains, supported by history of the use of oils. Treatment consists of discontinuing the use of the offending oil and rarely is surgical removal necessary.

RESUMEN

En este estudio las neumonías lipóidicas se clasifican en (1) exógenas, tales como los parafinomas o los granulomas debido a la aspiración de aceite mineral, vegetal o animal; y (2) endógenas (neumonitis de colesterol, granuloma de Wegener, etc.).

A la luz de estos factores etiológicos se revisan nueve casos de granuloma lipóidico tratados quirúrgicamente en los pasados 10 años. Todos habían sido clasificados previamente como granulomas aceitosos o parafinomas. De hecho la apariencia de las lesiones en ambos tipos se ven iguales para el observador ligero. Sin embargo los estudios histológicos revelaron que cinco de nuestros casos deben ser clasificados como endógenos.

La fuente de lípidos exógenos es obvia; la causa de depósitos de colesterol es más difícil de apreciar y las causas de posible presencia del colesterol se discuten. Parece que muchos granulomas de colesterol se reabsorben espontáneamente y sólo persisten las que han sufrido reacción desmoplástica severa. En éstos puede ser necesario la toracotomía si ocurre excavación grande.

Las lesiones de origen exógeno pueden diagnosticarse por repetidos exámenes de esputos con colorantes especiales, de acuerdo con el concimiento de que se han usado aceites.

El tratamiento consiste en la interrupción del uso de los aceites y rara vez la resección quirúrgica.

RESUME

Dans cette étude, les pneumonies lipoïdiques sont classées comme (1) d'origine exogène: paraffinomes ou granulomes huileux dû à l'aspiration d'huiles minérales, végétales ou animales; (2) d'origine endogène (pneumonie à cholestérol, granulome de Wegener, etc.).

Les auteurs font l'étude de neuf cas de granulome lipoïdique traités chirurgicalement dans les dix dernières années, à la lumière de nouveaux facteurs étiologiques. Tous avaient été d'abord classés comme granulomes huileux ou paraffinomes. Certes, la première impression que donnent les lésions appartenant aux deux types de pneumonies lipoïdiques peut sembler la même à l'observateur peu habitué. Cependant les études histologiques révélèrent que cinq de nos cas de vraient être classés comme d'origine endogène, plutôt qu'exogène.

La source des lipides exogènes est évidente; la cause de dépôts de cholestérol est plus difficile à évaluer et les auteurs discutent les différentes origines possibles de cette présence de cholestérol. Il semble probable que beaucoup de granulomes de cholestérol sont résorbés spontanément et que seules persistent les lésions qui se sont accompagnées d'une réaction importante. Celles-ci peuvent nécessiter une thoracotomie s'il survient un processus cavitaire extensif.

Les lésions d'origine exogène peuvent etre diagnostiquées par des analyses répétées d'expectoration et des colorations spéciales, basées sur ce que l'on peut apprendre au sujet des huiles utilisées par le malade.

ZUSAMMENFASSUNG

In der vorliegenden Untersuchung werden die Lipoidpneumonien eingeteilt in (1) exogene, in der Erscheinungsform von Paraffinomen oder Ölgranulomen als Folge einer Aspiration von mineral-pflanzlichem oder tierischen Öl, (2) endogen (Cholesterin-Pneumonitis, Wegener's Granulom usw.).

9 Fälle von Lipoidgranulomen, die in den vergangenen 10 Jahren chirurgisch behandelt wurden, werden im Licht der neuen ätiologischen Faktoren überprüft. Sie lale waren zuvor klassifiziert worden als Ölgranulome oder Parafnome. Tatsächlich mag das makroskopische Erscheinungsbild der Herde bei beiden Typen dem gelegentlichen Beobachter gleichartig erscheinen. Jedoch ergaben die histologischen Untersuchungen, dass man 5 unserer Fälle als endogene Lipoidpneumonien einreihen muss und nicht als exogen. Die Herkunft der exogenen Fette ist unklar; die Ursache der Cholesterinablagerungen ist schwierig zu ergründen, und es werden die möglichen Umstände für das Vorkommen von Cholesterin diskutiert. Es scheint möglich, dass viele Cholesterin-Granulome spontan absorbiert werden und nur die Herde bestehen bleiben, die zufällig zusammentreffen mit schweren desmoplastischen Reaktionen. Diese können eine Thorakotomie erfordern, falls es zu einer ausgedehnten Cavernisierung kommt.

Die Veränderungen exogener Natur kann man diagnostizieren durch wiederholte Sputumuntersuchungen und spezielle Färbemethoden, gestützt auf eine Vorgeschichte mit Gebrauch von Ölen. Die Behandlung besteht in der Beendigung der Verwendung der krankmachenden Öle; chirurgische Beseitigung ist selten notwendig.

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Chronic Pulmonary Suppuration

N. H. DEJANNEY, M.D., F.C.C.P. and OSCAR BIGMAN, M.D.*

Detroit, Michigan

The purpose of this paper is to focus attention on present antibiotic treatment of pulmonary suppurative disease, inasmuch as the current literature does not stress medical management. From the literature one receives the impression that in acute suppurative conditions of the lung surgical treatment is still the preferred method of management and that it should be instituted early. In fact, acute pulmonary abscess is still claimed to be a surgical problem from the beginning. While it is true that surgical intervention is required in some cases, it is also true that in other cases medical management alone renders surgery unnecessary. The authors hope that this article will indicate that the concept of surgery *a priori* as the proper treatment of pulmonary abscess is no longer true. Surgical treatment may be required—but not before medical treatment has first been tried and found to be incompletely effective. Although we believe that present day surgical opinion is no longer so restrictive, the literature does not make clear that a change in concept has occurred.

Although this discussion deals with suppurative disease of the lung in general, emphasis is given to lung abscess because that is *l'exemple par excellence* of pulmonary suppurative disease, concerning which so many articles have been written. In the literature great stress is given to preventing the acute condition from becoming chronic. But the dividing line between acute and chronic stages is at best a hazy and artificial one. Frequently the onset of illness can be only poorly established so that the transition into chronicity can be only poorly determined. Besides, with all the antibiotics that are freely administered today, the course of the disease is affected to a degree that makes the old dictum of six weeks the point where the acute stage ends, no longer true. Moreover, the importance of acute or chronic classification is further lessened by the fact that treatment, up to a certain point, is substantially the same.

A brief review of the literature at this point may be profitable. Allen and Blackman,[1] in a series of more than 2,000 cases, collected up to 1936, found a mortality of 34.4 per cent for the medically treated cases. However, the drop in mortality for the cases in the series that received surgical treatment in addition to medical care was only 0.2 per cent. Early surgery was the only means of further lowering this mortality. As early as 1920, Heuer[2] performed early drainage in a small group of cases with surprising success. This method became firmly established following the classic articles of Neuhof and Touroff[3] who advocated surgical drainage as the best therapy for the acute, putrid lung abscess. The early mortality of 35 per cent was reduced by them to 5 per cent and later to approximately 3 per cent. This led to the era when the diagnosis of lung abscess automatically indicated surgical treatment by drainage. There was general acceptance of their results and conclusions. We, also, agree with them—but only for

*From Chest Division, Herman Kiefer Hospital.

the period preceding the present era of antibiotics. D. T. Smith collected 2,166 cases between 1938 and 1948.[4] The mortality of medically treated cases was 34.7 per cent while the mortality among the surgically treated cases was 32.7 per cent. This is not a significant difference. Yet the surgical cases included the series of Neuhof and Touroff with only a 2.6 per cent mortality. This was exceptionally low and not approached by any other surgeon. If Neuhof's series is excluded the mortality rises to 40.4 per cent for the surgical group. Neuhof's series was selective, in that he excluded what he called, "acute suppurative bronchopneumonia." Smith believed that medical treatment was responsible for conditions resulting in the death of one third of the patients who developed primary pulmonary abscesses. In contrast to the surgical series the cases coming under medical management, more often than otherwise, were more complicated. Smith observed that surgically treated patients fared better than those treated medically. Yet in his study of collected cases, contrasting surgical versus medical treatment, there are 10 authors who appear in both groups. When a comparison is made we find that eight of these 20 had fewer deaths *not* in the surgical series, but in the medical series. (Figure 1.) It is obvious from these statistics, that one may be justified if he regards them with some degree of skepticism. On the other hand, it is true that in the surgical series, chronicity developed in 12.8 per cent fewer patients.

In April, 1948, Glover and Clagett[5] stated, "The advent of chemotherapy and the antibiotics has further tended to postpone a more definitively surgical attack, so that there is a tendency to revert to the so-called more conservative attitude in the hope that newer drugs can accomplish cures denied to earlier medical regimens." They undertook a study, the purpose of which was, "to forestall any such fallacious thought."

As late as January, 1954, Waterman and Domm,[6] said, "Statements contending that the antibiotics have made lung abscess entirely a medical problem are both fallacious and dangerous." Also, quoting further, "lung abscess is a surgical disease from the outset." The same authors, in May, 1955,[7] claimed that there are three fallacies commonly held by many physicians concerning lung abscess: (1) Lung abscess is so rare it is no longer of importance, (2) medical treatment alone suffices in practically all of the few cases encountered, (3) resection is the only surgical procedure to be considered in the remaining cases. We believe the first two of the fallacies mentioned above are exaggerated. Personally, we do not know anyone entertaining such ideas. As to the third fallacy—we do not believe it is a fallacy. It is a truism. In one recent article,[7] the above authors state, "while our over-all mortality, since antibiotics have been used, has been gratifyingly low, we have actually seen no decrease, but rather an increase

Authors	Number of Patients	Medical Mortality	Surgical Mortality
Allen & Blackman	2114	34.4%	34.2%
D. T. Smith	2166	34.7%	32.7%
D. T. Smith, excluding Neuhoff & Touroff	2014		40.4%

FIGURE 1

in the number of cases coming to surgery." On the other hand, Gittens and Mihaly,[8] have said "Lung abscess is definitely decreasing in incidence," and that, "the number of patients requiring surgery will become increasingly smaller, if prompt and adequate antibiotics and ancillary medical measures are instituted early in the course of acute suppurative disease." We believe that fewer lung abscesses are seen today, probably because ill patients are commonly treated early with penicillin or with other antibiotics. It should not be a maxim at present that acute suppuration indicates early surgical intervention. Under adequate medical management, the suppurative process will be either cured or rendered less hazardous for surgery. C. W. Holman,[9] early in 1950, pointed out that the "Complications of persistent bronchocutaneous fistula or bronchiectasis at the site of the previous abscess have long been recognized as serious objections to simple drainage." He believes early surgical drainage is rarely necessary, and instead, conservative treatment with antibiotics should be used first. The initial sepsis and toxicity is usually readily controlled by antibiotic treatment and satisfactory response may be expected. Some patients progress to complete recovery; others pass into a chronic phase for which resection will be required, but which will allow conservation of greater lung volume. Prior to April, 1949, Holman successfully shelled out the lung abscess in three cases, thus avoiding the sacrifice of the entire lobe. In April of the following year, B. J. Ryan[10] reported on 110 consecutive

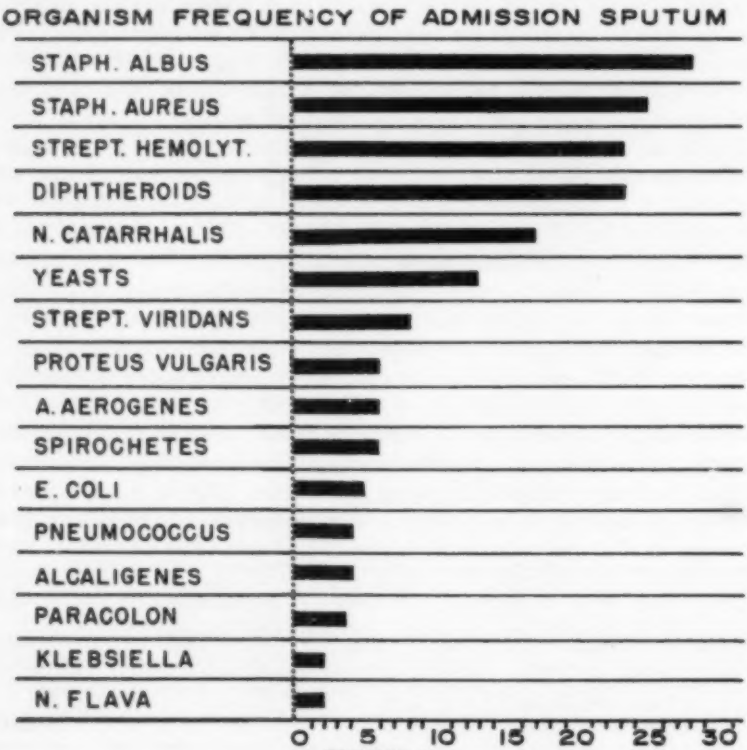

FIGURE 2

resections without operative mortality from May 1, 1946, to January 1, 1949. In three cases segmental resection only was done for chronic lung abscess. Such excellent results can only be obtained with the aid of chemotherapy. In March, 1954, Fox, Hughes, and Sutliff,[11] reported on 32 cases of lung abscess treated without benefit of surgery. Twenty-eight were cured; one improved; and one died.

In this discussion bronchiectasis is included as one of the suppurative processes. Simple bronchiectasis, in which infection is not the dominant condition, is excluded. Infected bronchiectasis, demonstrated by infection with expectoration of sputum, slight elevation of temperature, and evidence of pulmonary pathology by x-ray examination, is essentially a suppurative process.

In our cases, we have seen patients with slight bronchiectasis, who were admitted with few or no symptoms, clear up the infiltrations seen by x-ray when treated with antibiotics. Patients who have bronchiectasis should not be rushed into surgery simply because this condition is present. Resection should be reserved, however, for the patient who has extensive bronchiectasis, persistent hemoptysis, or severe hemorrhage—the patient who requires relief from the pathologic process of his disease.

There is merit to the statement of Wynn-Williams[12] that, "It may not be justifiable to advocate surgery whenever this is possible; a high proportion of bronchiectatic persons remain well and are little inconvenienced by their disease, if competently treated by postural drainage and antibiotics."

Frequently patients who presented themselves with lung abscess were found to have bronchiectasis. This was determined in some cases by bronchograms, when surgery was not done; and in other cases, where resection was performed, the pathologist reported bronchiectasis in the removed specimen.

Rosenblatt[13] notes the importance of bronchography to determine residual cavitation, which often is not readily seen by ordinary x-ray film exposure. We now try to do bronchography on all patients with suppurative disease prior to discharge.

	Penicillin	Tetracycline	Oxytetracycline	Chlortetracycline	Chloramphenicol	Erythromycin	Magnamycin	Streptomycin	Polymyxin
Staph. Aureus (C+)	R	R	R	R	S	S	S	R	R
N. Catarrhalis	R	S	S	S	S	R	R	R	R
H. Influenzae	S	S	S	S	S	S	S	R	R
Mixture	R	R	R	R	S	R	R	R	R

FIGURE 3

The cases in the present study form a selected group rather than the general run of cases seen in a non-specialty hospital. They are patients who were referred to us with the diagnosis of pulmonary tuberculosis, or, as tuberculosis suspects, and who, in reality, were suffering from lung abscess, bronchiectasis, or some other form of chronic pneumonitis. They were all managed in a similar manner so that, although they do not comprise a pathological entity, they do make up a clinical entity. In this series of 36 cases, the usually listed causes of suppuration, such as operative procedures on the oropharynx, were absent. There were eight chronic alcoholics, three epileptics, and two diabetics in the group. One had sustained significant chest wall trauma of the area that later developed an abscess. There was a marked preponderance of white (81 per cent) men (75 per cent) in the series. The age distribution ranged from the third to the eighth decade, with the majority falling in the age group from 35 to 65. Only one third of the group gave a history of previous major respiratory infection, usually pneumonia. Fourteen of the 36 had been inadequately and unsuccessfully treated with antibiotics prior to admission.

The most common symptoms were in decreasing order, productive cough, chest pain, weight loss, and fever. Dyspnea was reported in six and hemoptysis in 10, the latter sign almost wholly in patients with bronchiectasis. One complained only of arthritis on admission. Only 10 had an admitting temperature of over 101° F. Nineteen had significant leucocytosis. In 17 the tuberculin reaction was negative. Foul sputum was encountered in only four patients, probably indicating that physicians are less likely to confuse suppuration with tuberculosis, in the presence of foul sputum. Bronchoscopy revealed mucosal erythema or purulent secretions in 17 of the 26 (65 per cent) patients bronchoscoped. Roentgenograms showed a unilateral lesion in 30 of 36 patients.

Our policy, when suppurative disease is suspected, is to obtain a sputum specimen at the earliest opportunity, start penicillin immediately and then adjust the antibiotic in accordance with sensitivity studies. The organisms

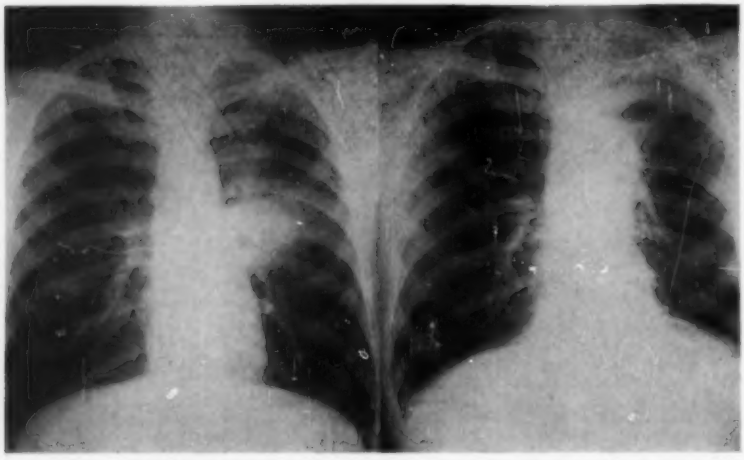

FIGURE 4A FIGURE 4B

commonly found in the sputum are frequently those considered not to be particularly pathogenic. The distribution we encountered is shown in Figure 2. To determine organism sensitivity to the various antibiotics we use the disc method, but realize fully its disadvantages. To run individual cultures on all organisms is too time consuming and requires a large laboratory staff, of a size which is not attainable at our institution. The disc method is a screening method of discovering which antibiotics are effective against the flora present. Sensitivity study is initiated as soon as the sputum is sent to the laboratory. Approximately 24 hours later the report is received and treatment with a suitable antibiotic is immediately begun. But the final bacteriological determination may require another 24 hours for final identification. If resistance to all common antibiotics is indicated, we will then subculture and determine the individual organism sensitivity. Figure 3 shows how the disc method may be misinforming. It is possible for the mixture to be totally resistant to all antibiotics because of overlapping of resistances. In this illustration the hemophilus is sensitive to many antibiotics which would not be suspected from the disc method, which shows only sensitivity to chloramphenicol.

Prolonged chemotherapy has been our policy. We have not infrequently watched a patient improve gradually over three months and occasionally over a six months period. We have recently seen a patient, not included in this series,* in whom a lung abscess secondary to bronchiectasis closed after more than one year of conservative management. However, we certainly do not advocate such prolonged treatment. In this case a diagnosis of pulmonary tuberculosis was made at another institution where the patient was hospitalized for six months. When the patient was transferred to us, we accepted the original diagnosis. There was slow, progressive clearing of a basal lesion of the left lung. During the entire period of hospitalization—before entering Kiefer, and while at Kiefer—no conclu-

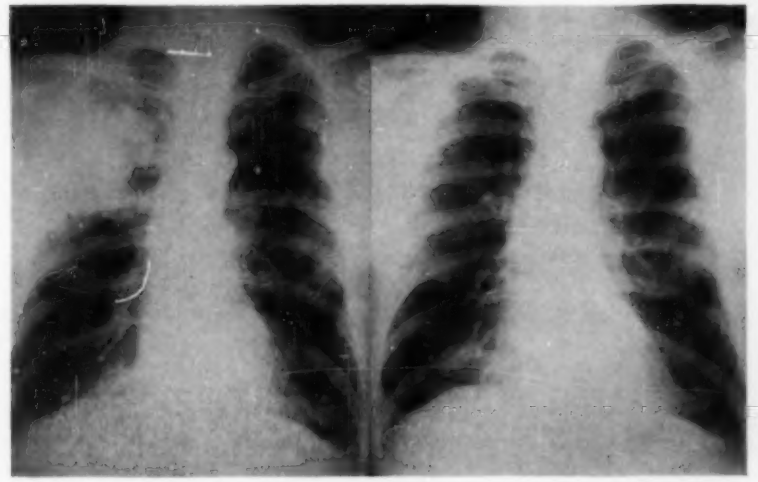

FIGURE 5A FIGURE 5B

*This case was studied after the series was completed.

sive proof of tuberculosis was found. Finally a bronchogram revealed the apparent tuberculosis infiltration to be due to bronchiectasis.

Early resection was performed only when we were uncertain whether we were or were not dealing with malignancy. Usually we have waited until a maximum response to medical treatment was obtained. Improvement may go on to complete resolution or may stop short of that desired goal. When resolution is incomplete, resection is advisable if the residual lesion is considered to be potentially hazardous to the patient's future health. In 21 of our patients, complete resolution occurred with medical management. The remainder had surgery. Ten were resected in less than three months, 4 in more than three months but less than six months, and one after six months. Eleven had one lobe or less resected, four had pneumonectomy (three of four bronchiectasis). There was no death among the surgical cases. Two patients expired, one of multiple brain abscesses, the other of pneumococcal meningitis.

Illustrative Case Summaries

Case 1: F. H. This 35 year old white man was admitted to HKH May 15, 1952, with a history of having caught cold nine weeks prior to admission. He developed slight cough and non-pleuritic left chest pain. Three injections of penicillin given him by his private physician failed to relieve symptoms. An x-ray film was taken and was considered compatible with pulmonary tuberculosis.

Admission temperature—99.4°F.; WBC—10,000; tuberculin—negative; diabetic glucose tolerance curve. Bacteriology: Pneumococcus Type C, E. coli, yeasts. Bronchoscopy: Left upper lobe orifice—slightly reddened. Treatment: Neopenil—May 28, to June 6, 1952: Chlortetracycline—June 16, to Juiy 14, 1952. Surgery: Left upper lobe resection June 30, 1952. Pathology: Chronic suppuration. Discharged July 16, 1952. Sixty-one days hospitalization.

Case 2: C. M. A 36 year old white man, was admitted on July 11, 1952, with a history of productive cough, fever, and right pleuritic chest pain starting suddenly the previous July. After three injections of penicilin, he felt better and returned to work. Early in October, he again became ill with fever and cough productive of large quantities of foul green sputum.

Admission temperature—102°F.; WBC—21,000; tuberculin—1+, 1:10,000; Bacteriology: Hemolytic streptococcus, B. aerogenes, B. proteus, Staphylococcus aureus. Treatment: Penicillin—July 16 to February 6, 1952; oxytetracycline—February 6 to February 28, 1952. Bronchoscopy: Normal. Surgery: Right middle lobe resection February 20, 1952. Pathology: Bronchiectasis and chronic suppuration. Fifty-five days hospitalization.

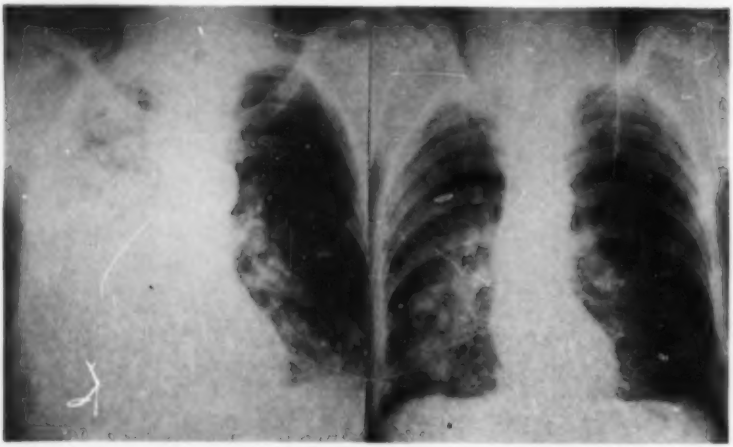

FIGURE 6A FIGURE 6B

Case 3 (Figure 4): F. S. This 52 year old man was admitted on September 14, 1951, with a history of left chest pain and dyspnea of two months duration. He had lost 24 pounds in the preceding nine months. He denied cough and hemoptysis.

Admission temperature—99.6°F.; WBC—12,400; tuberculin—negative 1:1,000: Bacteriology reported only paracolon from bronchoscopy. Bronchoscopy report missing. Surgery: Ten days after admission left upper lobe was resected because there was a strong suspicion that tumor was present. Pathologist reported chronic suppuration, purulent bronchitis and bronchiectasis. Twenty-four days hospitalization.

Case 4 (Figure 5): H. L. A 53 year old white man admitted April 1, 1953, with history of dyspnea for one week, productive cough and right pleuritic pain for one day. Fatigue for six months. Two years previously he had been in an auto accident. Several ribs had been broken and the lung punctured. He had had thoracotomy at that time.

Admission temperature—103°F.; WBC—15,000; hemoglobin—12.5 gm.; tuberculin—negative. Bacteriology: Streptococci and Staphylococcus albus. Treated with chlortetracycline and chloromycetin with good clearing of lesion. Discharged after 107 days of hospitalization.

Case 5: E. Y. This 30 year old white man, was well until two months prior to admission, when he began to have painful swelling of both knees and both ankles. In retrospect he recalled a severe cold with cough and fever three months before. He lost 15 pounds and felt tired. He was unsuccessfully treated for rheumatoid arthritis by his own physician until a routine chest film showed a pulmonary lesion.

Past History: Pleurisy two years before. Convulsions for two years—last episode three months prior to admission.

Physical Examination: Clubbing of fingers. Admission temperature—99.8°F.; WBC—17,900; Hemoglobin—normal. On treatment with penicillin followed by chloramphenicol, both the chest lesion and the osteoarthropathy improved, and he was discharged 34 days after admission, asymptomatic.

Case 6: M. E. A 33 year old negress admitted July 23, 1954, with a one month history of productive cough, weight loss, fever and hoarseness. She was treated with penicillin for three weeks at another hospital before transfer here.

Admission temperature—99.4°F.; WBC—9,900; hemoglobin—13.9 gms.; tuberculin—2+. Bacteriology: Streptococcus pyogenes, Staphylococcus albus (C—), A, aerogenes, diptheriods, N. catarrhalis. Bronchoscopy: Negative. Bronchograms: Negative. Treated with penicillin with clearing. Discharged 58 days after admission.

Case 7 (Figure 6): J. M. This 72 year old white man was admitted May 3, 1952, critically ill, unable to give a history.

Admission temperature—100°F; WBC—11,750; tuberculin—negative. Bacteriology: B. proteus, staphylococcus albus, diptheroids, fusiforms, sensitive only to chloramphenicol and oxytetracycline. Later studies showed similar organisms, but they were sensitive to chlortetracycline and oxytetracycline only. Bronchoscopy: Narrowing of right main bronchus July 2, 1952; repeated on July 16, 1952, and reported as showing much less narrowing. Treatment: Penicillin May 13 to May 20, 1952. Chloramphenicol May 20 to June 24, 1952, and chlortetracycline July 2 to July 28, 1952. After considerable clearing, he was transferred to a general hospital. Eighty-seven days hospitalization.

FIGURE 7A FIGURE 7B

Case 8: L. P. This white woman, 68 years old, was admitted July 22, 1953, with a history of having caught cold seven months before, following which she developed progressive weakness and chronic cough. In June, 1953, she had coughed up blood. She had pneumonia in 1943.

Admission temperature—98.8°F.; WBC—7,000; tuberculin—positive only in 1:100 dilution. Bacteriology: alkaligenes, diphtheroids, Streptococcus pyogenes, Staphylococcus aureus. Bronchoscopy: Edema of right main stem bronchus. Treated with chloramphenicol and streptomycin with good results. Discharged 44 days after admission.

Case 9 (Figure 7): W. S. This white man, 53 years old, was admitted July 31, 1951, with history of weakness and weight loss over a two months period.

Admission temperature—99°F.; WBC—14,600; moderate anemia; tuberculin—negative. Bacteriology: Staphylococcus albus, Hemolytic streptococcus. Treated with penicillin alone. The lesion cleared well, and he was discharged 45 days after admission.

Discussion

From the literature, it seems that there are two schools of thought regarding the treatment of pulmonary suppurative disease. The first regards suppurative disease—best exemplified by lung abscess—as a surgical problem from the outset. The second, that it is a medical problem. Among the supporters of the first group, there would seem to be some confused thinking. In practice they actually are using combined medicosurgical treatment. It would appear, then, that the proponents of surgical treatment would routinely do some resection after the patient has had the benefit of some medical management.

We believe that surgery should be considered secondarily—only after proper medical management has been used and has fallen short of cure. The end result of medical therapy alone may obviate the need for surgery, or, if the scalpel is still required, the result will be better and performed more safely.

The role of surgery is not being minimized, but, we should recognize the great advances made in medical management of the patient with suppurative disease.

We wish to emphasize that it is difficult for us to think of patients as surgical or medical cases. At first, they are neither—for we do not know what the result of medical management will be. They are simply patients to be treated, and, if possible, made well; and, the first part of the treatment must be medical. Whether it remains strictly medical or will encompass surgical treatment also, will depend upon the course of the disease.

We believe that the antibiotics available today have entirely changed the surgical treatment of pulmonary suppurative disease. With more patients surviving the acute stage of suppurative disease, the problem of treatment of the chronic stage becomes ever more important. We do not believe that pulmonary suppurative disease in the acute or chronic stage should be regarded as either medical or surgical. Our attitude is that this condition be approached medically, and as long as improvement continues, it should be allowed to go on.

CONCLUSION

1. Pulmonary suppurative disease is not primarily a surgical condition. It should always be treated medically initially. Whether or not surgical intervention will follow will be determined by the changes that occur in each case.
2. Bronchoscopy is indicated in almost every case, and may be used both diagnostically and therapeutically.
3. The laboratory should determine the pathogenic organism preferably from the bronchial secretions. Suitable antibiotics should be chosen on the basis of sensitivity study.
4. A lesion that is unresolved after a period of treatment, considered to be adequate, should be resected. In those cases where the suppurative process has resolved, but a slight degree of bronchiectasis persists with few or no symptom, resection should not be done.
5. Bronchographic study should be made in every case. This is of importance not only in the current therapy, but also as a reference point if there is recurrence of illness.

CONCLUSIONES

1. La supuración pulmonar en principio no es un padecimiento quirúrgico. Siempre debe tratarse médicamente al principio. Si se ha de usar o no más tarde la cirugía será de determinarse más tarde según la evolución.
2. La broncoscopía está indicada en casi todos los casos y puede usarse con fines diagnóstico y terapéutico.
3. El laboratorio determinará el organismo patógeno de preferencia a partir de las secreciones bronquiales. Deben escogerse los antibióticos necesarios según las pruebas de sensibilidad de los gérmenes a ellos.
4. Una lesión que no se resuelve después de cierto período de tratamiento que se considere adecuado, debe resecarse. En los casos en que el proceso supurante se ha

resuelto pero persiste la bronquiectasia en cierto grado con pocos o ningunos síntomas, la resección no debe hacerse.

5. Debe hacerse estudio broncográfico en todos los casos. Esto es de importancia no sólo en la actualidad, sino como punto de comparación para las recurrencias.

RESUME

1. Les suppurations pulmonaires ne constituent pas d'emblée une indication chirurgicale. Elles devraient toujours être traitées d'abord médicalement. L'intervention chirurgicale éventuelle sera déterminée par l'évolution de chaque cas.

2. La bronchoscopie est indiquée dans presque tous les cas, et peut être utilisée à la fois dans un but diagnostic et thérapeutique.

3. Le laboratoire devrait déterminer le microbe pathogène recueilli de préférence dans les sécrétions bronchiques. Des antibiotiques convenables devraient être choisis sur la base de l'étude de la sensibilité.

4. Une lésion qui ne s'est pas améliorée après une période de traitement considérée comme adéquate, devrait être réséquée. Dans les cas où le processus suppuratif a été jugulé, mais où il persiste un certain degré de bronchectasie avec peu ou pas de symptomes, la résection devrait être pratiquée.

5. Une étude bronchographique devrait être faite dans chaque cas. Elle est importante non seulement en thérapeutique courante, mais aussi comme élément de référence s'il y a récidive de l'affection.

ZUSAMMENFASSUNG

1. Eine eitrige Lungenerkrankung ist nicht in erster Linie ein chirurgisch zu behandelnder Krankheitszustand. Sie muss immer zuerst internistisch angegangen werden. Ob ein chirurgischer Eingriff angeschlossen werden soll oder nicht, hängt ab von den Veränderungen, die sich im Einzelfall ereignen.

2. Eine Bronchoskopie ist fast in jedem Fall angezeigt und kann sowohl diagnostisch als auch therapeutisch von Nutzen sein.

3. Im Laboratorium müssen die pathogenen Keime vorzugsweise des Bronchialsekretes analysiert werden. Entsprechende Antibiotica müssen auf der Basis von Sensibilitätsprüfungen gewählt werden.

4. Eine Verdichtung, die nach einer als adequat anzusehenden Behandlungsperiode sich nicht gelöst hat, muss reseziert werden. In den Fällen, in denen sich der eitrige Prozess resotbiert hat, jedoch ein leichter Grad von Bronchiektasie bestehen bleibt mit wenig oder keinen Symptom, sollte nicht reseziert werden.

5. Bronchografische Untersuchungen müssen in jedem Fall unternommen werden. Das ist von Wichtigkeit nicht nur für die laufende Behandlung, sondern auch als ein Merkzeichen, wenn es zu einem Rückfall der Erkrankung kommt.

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Pulmonary Tuberculosis in the University of Malaya Students

Z. N. KADRI, M.D., F.C.C.P.

Singapore, Malaya

The University of Malaya was established in October, 1949, as a national institution to serve the higher educational needs of the Federation of Malaya and Singapore. A scheme for routine clinical examination of all freshmen, on a voluntary basis, was initiated in October 1952, whereas compulsory radiographic examination of the chest at the time of entry into the University was introduced in October 1954. In the absence of any controlled survey in either territory, it is not possible to indicate the incidence of tuberculosis in the general population. But it is common knowledge that morbidity and mortality from this disease, despite increasingly widespread use of antibacterial therapy, is much higher in this part of the world than in any western country, irrespective of the age. As in America, it is our impression that the greater number of active cases is found in older age groups who form the reservoir of infection.

In this paper, we report the incidence of tuberculosis and its rate of recurrence of activity in students of all faculties of the University, over a five academic year period beginning in September 1953, and ending in May 1958. Freshmen who gained entry in the 1953 academic session were subjected to radiographic examination soon after admission. All successive batches of students entering from 1954 to 1957 submitted chest films prior to admission, through their respective private physicians. Most of the entrance skiagrams were large films. It has been our policy to examine all the students with photofluorographs (4″ x 5″) twice or thrice during their University career, full size films being made of cases showing doubtful shadows. Every suspicious-looking new shadow was fully investigated for tuberculosis, the activity of which was determined by close radiological follow up, sputum or gastric lavage cultures for tubercle bacilli, blood sedimentation rates and tomograms. In the absence of any sanctions, it is not possible to enforce compulsory periodic x-ray film examinations. Nevertheless, response from the students has been increasing steadily, and a greater number of them are coming forward voluntarily every year. All follow-up photofluorographs or large films in this study were initially interpreted by a radiologist in the X-ray Department of the Government Tan Tock Seng Chest Hospital, and rechecked by the author.

Within the past five years 1834 freshmen have come under surveillance and 3450 films have been obtained. All 1834 students have had at least one x-ray film, either before matriculation or during the course of their academic career. In this study, almost all the students who were enrolled in 1953 and 1954 sessions, have by now left, after completing University education. They therefore came under surveillance for the entire span of their academic career, whereas freshmen admitted in 1957 have been observed for a period of only one year.

Department of Student Health, University of Malaya.

In a study of tuberculosis in foreign students entering Ohio State University, W. T. Palchanis found 11.7 per cent had inactive pulmonary lesions at the time of their enrolment. During his 17 months study of the group, 18.7 per cent of foreign students, mainly of Asian extract, harboring inactive disease, developed activity; while during the same period, none of the 0.44 per cent of students from the United States having inactive tuberculosis at the time of entrance became active. In a study conducted at the Florida State University beginning in September 1949 and ending in July 1952, the overall incidence of tuberculosis was estimated to be in the region of 0.4 per cent. In Verney's Survey of tuberculosis in the student population of British Universities, the average incidence was found to be 0.25 per cent. Data on the rate of recurrence of activity are not available in this report.

On the basis of our study by x-ray films plus the application of additional diagnostic measures wherever indicated, 49 (2.67 per cent) of 1834 freshmen admitted during the five year period were known to have inactive lesions at the time of entry, whereas nine (0.48 per cent) students with known clear lungs developed new lesions during the course of study. Among 49 known inactive cases 13 reactivated while at the University. In short, 26.5 per cent of old cases relapsed under the usual stress and strain of college education, requiring treatment in the form of rest, antibacterial chemotherapy, and in two cases surgical intervention. Education was interrupted in most of the active cases for periods varying from three to 12 months, but none was obliged to quit the University permanently. Some of these inactive cases are still attending the University and are under observation and it is therefore not possible to make a final assessment of the rate of recrudescence of tuberculosis at this stage. Nevertheless, the relapse rate of 26.5 per cent may be considered quite high, in view of the fact that all precautions were taken to exclude active cases from participating in University education, and entry was confined to those cases which fulfilled the criteria of inactivity for at least six months as laid down by the American National Tuberculosis Association.

Of the three main races inhabiting the Federation of Malaya and Singapore, the Malaysians are the indigenous people of Polynesian extract and constitute about half the population of Malaya.* If both the territories were taken into consideration, the numerical strength of Malaysians would be in the region of 42.7 per cent, the majority of whom are paddy farmers living in villages (kampongs) in the rural districts. Among the immigrant races, the Chinese, who tend to be urban dwellers, form 44.2 per cent of the combined population of both the territories, while 11.6 per cent of the inhabitants belong to the stock whose origin can be traced to India, Ceylon or Pakistan. Compared to the well-established western universities, our institution is young and small, nevertheless, its multi-racial character extends an interesting opportunity for the study of ethnic influences on tuberculosis. Although the Malaysians constitute the majority of the population in the Federation of Malaya, their percentage in the University over the period of this study has been in the region of 13 to 14 per cent. By contrast, Indians, under which heading Ceylonese and Pakistanis are

*Population percentages are based on mid 1955 statistics.

included, despite their smaller number in the general population, have contributed a commensurately higher number of students to the University education. As far as the figures in our study go, there is clearly no significant difference in the incidence and relapse rate of tuberculosis in the different ethnological groups. Furthermore, although it is the author's impression, gathered from study of tuberculosis in the general population, that the Malaysians mostly develop exudative lesions, whereas in the Chinese the lesions are inclined to exhibit fibrotic features, no significant variation in the pattern of reaction to disease was found in students belonging to various races.

Palchanis, discovered that 81.2 per cent of South East Asian students at the Ohio State University were tuberculin reactors, this being in sharp contrast to only 16.5 per cent of American students mostly from Ohio, who reacted to tuberculin. According to Verney 66 to 75 per cent of British University students were found to yield a positive response to tuberculin.

In the program of testing tuberculin sensitivity conducted in Singapore in 1951 on school children and adults by the U.N.I.C.E.F./WHO team, 48 per cent were found to react at the age of seven years, and as many as 77 per cent at the age of 15 years. It was also noted that by the age of 30 years nearly all individuals were Mantoux positive. Tuberculin sensitivity tests were first introduced in the University of Malaya in 1953, but were confined to medical students about to embark on clinical work. Mantoux tests, consisting of 10 tuberculin units, that is 0.1 cc. of 1/1000 old tuberculin units were employed during the early part of the study. Those who did not react were retested with higher concentration. All reactions with a diameter of induration less than 5 mms. were deemed to fall into the negative group. For the past three years this method has been replaced by Heaf's multi-puncture method, which in our opinion, is safe, more reliable and faster to execute. Since 1957, the program has been extended to include freshmen of all the faculties studying in the Singapore Division of the University, and medical students in all the years. In all 488 students have thus far been subjected to either method, out of whom 460 or 94.3 per cent were found to be positive reactors, the 28 negative reactors received BCG.

SUMMARY

The overall incidence of clinical pulmonary tuberculosis in the University of Malaya students was found to be 3.15 per cent.

This higher incidence of clinical tuberculosis is in keeping with the general morbidity and mortality figures of tuberculosis in the general public.

Among students who were originally enrolled as inactive cases 26.5 per cent developed activity while in university and required treatment.

No significant difference was found in the incidence and rate of reactivation of disease in students of various races.

No student was obliged to quit studies permanently on account of the breakdown.

RESUMEN

La incidencia general de la tuberculosis pulmonar clínica en los estudiantes de la Universidad de Malaya, se encontró de 3.15 por ciento. Esta más alta incidencia de la tuberculosis clínica está en relación con la morbilidad más alta y la mayor morbilidad por tuberculosis en el público.

Entre los estudiantes que originalmente empezaron sus estudios como casos inactivos, 26.5 por ciento se tornaron activos mientras estaban en la escuela y requirieron tratamiento.

No se encontró diferencia significante entre la frecuencia de la reactivación de la enfermedad en estudiantes de diversas razas.

Ningún estudiante fué obligado a abandonar los estudios a causa de su reactivación.

RESUME

On a constaté que la fréquence moyenne de tuberculose pulmonaire clinique chez les étudiants de l'Université de Malaya était de 3,15%. Cette grande fréquence de la tuberculose clinique est en relation avec les chiffres de morbidité générale et de mortalité par tuberculose dans la population.

Sur les étudiants qui furent d'abord recensés comme cas inactifs, 26,5% se montrèrent évolutifs alors qu'ils étaient en période scolaire et nécessitèrent un traitement. Il n'y eut pas de différence profonde entre la fréquence et le taux de réactivation de la maladie chez les étudiants de races différentes. Aucun étudiant ne fut obligé de renoncer définitivement à ses études par suite de l'interruption due à la maladie.

ZUSAMMENFASSUNG

Die Gesamt-Häufigkeit klinischer Fälle von Lungentuberculose unter den Studierenden der Universität von Malaya wurde mit 3,15% ermittelt. Diese grössere Häufigkeit von klinischer Tuberkulose stimmt überein mit den Werten der Morbidität und Mortalität an Tuberkulose unter der Gesamtbevölkerung.

Unter den Studierenden, die ursprünglich als inaktive Fälle geführt wurden, entwickelten sich 26,7% aktive Befunde während der Ausbildung und benötigten Behandlung. Es wurden keine ins Gewicht fallende Differenzen ermittelt im Vorkommen und in der Zahl von Reaktivierungen bei Stundierenden der verschiedenen Rassen. Kein Student war genötigt, wegen seiner Erkrankung die Ausbildung für immer aufzugeben.

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Pulmonary Embolism by Amniotic Fluid

R. J. SHELLEY, M.D.,* A. D. DENNISON, JR., M.D., F.C.C.P.**
and J. V. THOMPSON, M.D., F.C.C.P.†

Indianapolis, Indiana

Amniotic fluid embolism was first described by Steiner and Lushbaugh in 1941.[1] Although the clinical picture is said to have been recognized previously, it was not until their work appeared that the entity was clearly understood.[2] They reported eight patients with similar clinical courses and autopsy findings. They also were able to reproduce this condition in dogs and rabbits by the intravenous infusion of amniotic fluid. In the years since, several excellent papers have been published on this subject. The clinical picture in all cases published to date is one of marked respiratory distress, with anaphylactoid shock, followed within a few hours by a generalized bleeding tendency in those patients who survive the initial insult. To support our belief that all degrees of severity of this clinical entity are possible, to present a definitive plan of therapy, and to increase the awareness of this problem in those interested in cardio-pulmonary disease, we present the following case report and discussion.

Case Report

The patient was a 29 year old married white woman, gravida 2, para 0. She was admitted to the labor room of the Indianapolis Methodist Hospital on the service of Dr. G. C. Boling at 11:15 p.m. on November 26, 1955. There was no history of congenital, rheumatic or other form of heart disease. Her initial pre-natal examination had failed to reveal any evidence of cardio-pulmonary disease. The antenatal course had been uneventful until the evening prior to admission, when she began to note seepage of fluid from the vagina.

The admission examination revealed a temperature of 100°F., a blood pressure of 138/64 mm. of Hg. and the pulse rate ranged between 100 and 118 per minute. The fetal heart tones were not heard, and it was believed that the fetus was dead. Antibiotic therapy was administered because of the prematurely ruptured membranes.

After a hard labor, she was delivered easily at 8:49 a.m. on the day after admission, by means of low forceps with episiotomy. The infant was a stillborn boy, weighing six pounds. The body was coated with meconium. At the time of delivery, it was at first thought by the anesthesiologist in attendance that she had aspirated vomitus; however, after repeated aspirations of the airways, he decided that this had not occurred. She was kept on the delivery table in Trendelenburg position until 9:45 a.m. because of hypotension. During this time her blood pressure ranged from 80/50 to 100/60 mm. of Hg.

At 9:45 a.m. she was taken to the obstetrical recovery room when the blood pressure was 88/55 mm. of Hg., the pulse rate was 112 and the respiratory rate was 24 per minute. She was coughing occasionally, but auscultation disclosed no râles. One-half hour later the cough became worse, she was pale, and respirations were noisy. A slow intravenous infusion of 1000 cc. of 5 per cent glucose in distilled water was begun. At 10:25 a.m. she was apprehensive, restless, coughing and cyanotic. Coarse râles were heard throughout the lung fields. Within an hour, respirations were rapid and labored, the skin was moist and pale, and the blood pressure was 86/60 mm. of Hg. Oxygen was started by nasal catheter.

She was seen in consultation by one of the authors, (A.D.D., a cardiologist), three hours after delivery. The skin was pale, moist and cyanotic. Respirations were tachypneic and labored, and the cough was extremely distressing. The blood pressure was unobtainable. The pulse was rapid and barely palpable. The heart sounds were completely obscured by coarse moist râles which were present throughout the thorax.

*Chief Resident in Obstetrics and Gynecology.
**Attending Cardiologist.
†Attending Thoracic Surgeon.
From The Methodist Hospital.

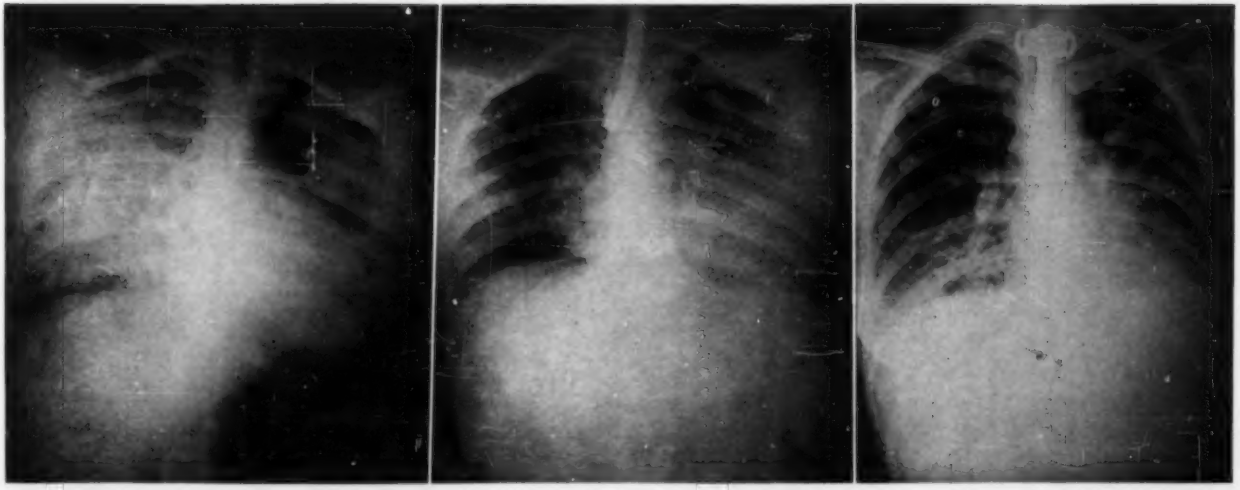

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Bedside roentgenogram taken 3 hours postpartum.—*Figure 2:* Bedside roentgenogram taken on the fourth post-partum day.—*Figure 3:* Roentgenogram on the eight post-partum day.

There was no evidence of bleeding from the vagina, mucous membranes or venipuncture sites. A portable roentgenogram of the chest (Fig. 1), obtained suggested extensive diffuse bilateral pulmonary edema. An intravenous infusion of 5 per cent glucose in distilled water containing 8 mg. of Levophed® and 100 mg. of hydrocortisone was started at a slow rate. At the same time, she received 250 cc. of pooled plasma. Penicillin and streptomycin therapy was instituted. Digitalization was carried out by the intravenous route. At this time a tentative diagnosis of amniotic fluid embolism was made. Throughout the afternoon her condition improved slightly, although she remained dyspneic.

During the following 36 hours the systolic blood pressure was maintained between 80 and 120 and the diastolic between 0 and 100 mm. of Hg., with the use of intravenous Levophed.® She received no further steroid therapy. On the second day, there seemed to be very little improvement until an antihistamine (Histadyl,® 50 mg. intramuscularly every six hours) was administered and a tracheotomy was performed by one of the authors, (J. V. T.) to permit effective aspiration of the airway, and to improve the ventilation. Aspiration of the trachea and bronchi at the time of tracheotomy produced copious amounts of pinkish froth. The aspirated material was sent to the histology laboratory and found to contain no foreign material. Following this, the respiratory rate fell from an average of 60 to 48 per minute. There was improved aeration of the lungs, and a decrease in the number of pulmonary rales present.

During the fourth and fifth days, she received 500 cc. of whole blood. Oxygen was discontinued on the seventh postpartum day, and the tracheotomy tube removed on the eighth day. Antibiotics were discontinued on the 10th day, while digitalis and antihistamines were continued until the 16th day. On the seventh postpartum day, a diagnostic bronchoscopy was done, which revealed only a slightly reddened right lower bronchial mucosa. No foreign material was aspirated from the bronchial tree. Serial roentgenograms demonstrated the gradual clearing of her lung fields (Figures 2 to 5).

The coagulation time (Lee and White) on the second postpartum day was normal and there was no subsequent clot lysis. Fibrinogen levels were within qualitatively normal limits at this time and on the subsequent day. Repeated electrolyte studies over the first 10 days of her hospitalization were within normal levels. Routine agglutination studies were normal, and sputum examinations disclosed no tubercle bacilli. An electrocardiogram on November 28 showed sinus tachycardia and nonspecific T and ST segment changes, suggestive of myocardial ischemia, and was within normal limits when repeated 10 days later. She was discharged on her 23rd postpartum day. Residual minimal pulmonary changes subsequently were resolved, as demonstrated on roentgenograms made following discharge from the hospital.

Incidence

Amniotic fluid embolism is generally conceded to occur once in every 8,000 deliveries. Graham,[3] in 1955, was able to collect 57 cases from

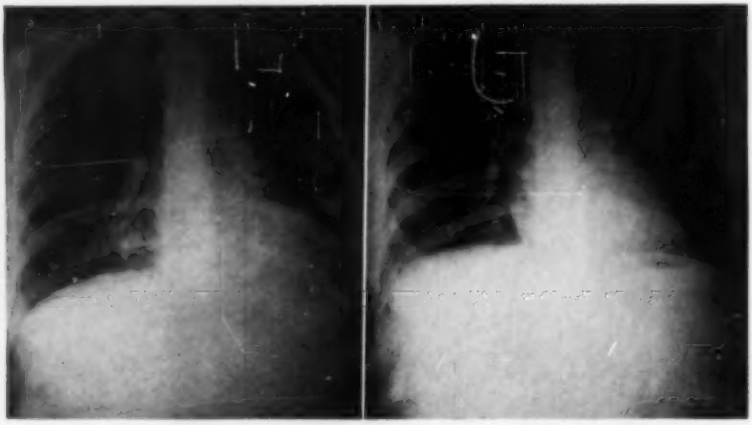

FIGURE 4 FIGURE 5

Figure 4: Roentgenogram taken on the 20th post-partum day.—*Figure 5:* Roentgenogram taken five months post-partum.

the literature. At the Indianapolis Methodist Hospital, from 1943 through 1955, there were 65,400 deliveries. During the same period, there were four deaths due to amniotic fluid embolism which were verified by autopsy findings. An additional four patients followed a similar clinical course and died, but autopsy was refused. Assuming these last four deaths were due to amniotic fluid embolism, the incidence of this entity at Methodist Hospital coincided roughly with the nationally reported incidence of 1 in 8,000 deliveries.

Pathogenesis

This type of embolism usually develops in the older multiparous patient. In many cases the fetus is dead, the membranes have ruptured, and meconium is present in the amniotic fluid. Labor is characteristically hard, and may even be violent. Frequently the fetus is past term and may be excessively large.

Amniotic fluid and debris (lanugo, vernix caseosa, desquamated squamous cells and meconium) enter the maternal circulation by several mechanisms.[4] With the membranes ruptured, and the breech or head blocking the cervical os, fluid and debris are forced out of the amniotic sac.

One of the earliest explanations was that the fluid, under pressure of uterine contractions, is forced out between the chorion levae and decidua. From there it dissects toward the placental site, where it enters one or more of the uterine sinuses.

The second, and possibly more likely mechanism, is by way of the endocervical veins.[5] These vessels become lacerated during labor, and account for the bloody show. As the cervix effaces, its upper portion is thought to become incorporated in the lower uterine segment, and the latter retracts over the presenting part. Some of the endocervical vessels are then exposed to amniotic fluid under pressure, and the fluid is forced into the maternal circulation.

Amniotic fluid may also enter the uterine sinuses during caesarian section, rupture of the uterus, and in the presence of placenta accreta.[4] There is no report in the literature concerning the presence of amniotic fluid debris in uterine vessels in association with a normal placental site.

Regardless of the route or mechanism of entry, once in the maternal blood stream, the amniotic fluid and particulate matter are carried to the pulmonary vascular bed, where vessels under 1 mm. in diameter are occluded. This course of events produces the clinical picture of disseminated pulmonary embolism.

Clinical Aspects

The first manifestations of the process are acute respiratory distress and shock. These develop during labor, parturition or the early postpartum period. The early symptoms are cough, restlessness, anxiety, nausea, vomiting, chills and dyspnea. These symptoms are followed by a rapidly developing shock with hypotension and tachycardia. Cyanosis appears quickly. Coma and/or death may occur within minutes or a few hours. The shock which is present often cannot be attributed to blood lost during the delivery, and is seen before any bleeding tendency develops. The physical findings of pulmonary edema are present. The cough may be productive of a frothy pink sputum.

Hemorrhagic Phase

If the patient survives the initial shock, then the second manifestation of amniotic fluid embolism usually occurs. This is the bleeding tendency which appears from three to six hours after the initial embolism. It was originally thought that the shock resulted in uterine atony with subsequent uterine hemorrhage. Reid, Weiner, and Roby,[6] however, have shown that the postpartum hemorrhage may be due to a fibrinogenopenia, rather than to uterine atony. They found that amniotic fluid contained a thromplastin-like material, the coagulative activity of which depended upon the concentration, rate, and amount of auto-infusion. Small amounts infused over a long period resulted in defibrinogenation of the blood, by deposition of minute clots in the maternal vascular system. Large amounts infused quickly produced an anaphylactoid reaction followed by a generalized bleeding tendency from the uterus, episiotomy, venipuncture sites and mucous membranes.

In addition to the intravascular coagulation phenomenon which occurs, a circulating fibrinolysin is present. This is believed to be produced by the body in response to the fibrin deposition associated with the intra-vascular clotting. Thus, when there is sufficient fibrinogen to form a clot, the lytic activity of the fibrinolysin is exerted and the clot tends to dissolve.

Should the patient expire and autopsy be refused, the diagnosis may sometimes be made from blood aspirated from the right ventricle. This sample is centrifuged, separating it into the red cell component and a layer of white cells, above which is a buffy coat rich in amniotic fluid debris.[7]

Discussion

The patient being presented had no bleeding; hence, one is presented with a differential diagnostic problem consisting of respiratory distress and shock in the early postpartum period.

All forms of pulmonary embolization should be considered. Vascular emboli occur later in the puerperium with the maximum incidence being between the ninth and 14th days. These are usually preceded by evidence of venous thrombosis. Thoracic pain is often present along with blood-tinged sputum. A pleural friction rub may appear sometime later, and there may be radiologic evidence of infarction. Embolization by placental or decidual tissue fragments is possible. They may simulate vascular emboli, but appear early in the postpartum period. This phenomenon may be ruled out on the basis of roentgenographic findings of a diffuse, bilateral process rather than one which is localized. Pulmonary air embolus at delivery is rare, and may be excluded by the absence of the churning or waterwheel murmur.

Aspiration pneumonitis must enter into the differential diagnosis, since it may occur at the time of delivery and produce symptoms in the first 12 hours, depending upon the nature and quantity of the aspirated material. Hydrochloric acid is usually conceded to produce the severe irritative reaction. This entity has a similar clinical course to amniotic fluid embolism, i.e., acute respiratory distress. In most instances, however, the patient is improving by the time the diagnosis is made[8] and the history is usually conclusive.

All forms of myocarditis must be considered, since they may be the basis for acute cardiac decompensation. Rheumatic myocarditis can be excluded by the absence of a history of rheumatic fever, lack of evidence for valvular pathology during pregnancy, or during follow-up examinations. Other forms of myocarditis may be eliminated by the absence of a gallop rhythm, serial electrocardiographic changes, and a known etiologic factor.

Congenital heart disease can be differentiated for similar reasons, i.e., no antenatal or subsequent evidence of cardiac pathology.

Idiopathic postpartal heart disease usually occurs two to six weeks postpartum. It is more often seen in negroes and in women who have had pre-eclampsia during pregnancy, or who have a long-standing history of inadequate nutrition. The onset is insidious, with dyspnea being mild rather than severe.[9] Fiedler's myocarditis has

similar onset, as well as much the same clinical picture and pathologic findings as the foregoing, but does not have the same predilection for the postpartum period.[9]

Pericarditis may be excluded due to the lack of the typical clinical symptoms, physical findings and radiologic evidence.

Cardiac failure secondary to toxemia of pregnancy should be included in the differential diagnosis. This condition, however, is characterized by the presence of hypertension, albuminuria or edema during pregnancy. Cardiac failure due to toxemia is usually seen in the late phases of eclampsia, as a terminal event.

Peripheral vascular collapse due to acute adrenal insufficiency must be included in the consideration, but may be ruled out on the basis of early presence of acute respiratory distress and pulmonary edema, followed by peripheral vascular collapse. Dyspnea, cyanosis, cough and restlessness are not seen with adrenal insufficiency.

Our patient never developed any bleeding tendency. Her hematologic studies were all within normal limits. Thus, the problem arose of justifying a diagnosis of amniotic fluid embolism in the absence of demonstrable fibrinogenopenia. Amniotic fluid embolism has been thought to be associated with a bleeding tendency, due to reduction of circulating fibrinogen. At the present time, however, there is some evidence to suggest that such an association may be not always clinically evident. For example, Hunter and associates,[10] in a preliminary study of experimental amniotic fluid embolism, were unable to produce hemorrhage in two dogs, following intravenous infusion of the animals' own respective amniotic fluid. This is in complete accord with the feeling of the authors, that all degrees of this entity are possible.

Treatment

The treatment of amniotic fluid embolism is supportive and definitive. Supportive therapy is generally supplied while the diagnosis is being made, and consists of vasopressor agents, aminophylline, adrenal cortical steroids and antihistamines, for the anaphylactoid shock reaction. Digitalis may be indicated for improvement of myocardial function. Intravenous fluids should be kept to a minimum, because of the existing or impending pulmonary edema. Oxygen, tracheostomy and intermittent positive pressure breathing are of invaluable aid in controlling the respiratory difficulty.

Definitive therapy is reserved for the hemorrhagic phase, when present. This should consist of fibrinogen replacement, when plasma fibrinogen levels are found to be decreased. Whole blood transfusions should be given as needed, keeping in mind the possibility of overloading the cardiovascular system. Pooled plasma, although not a very satisfactory substitute, may be used in the absence of fibrinogen, since it has an average fibrinogen level of 0.35 mg. per cent, even when stored for three year periods.[11] It is suggested that, where low fibrinogen levels are suspected, volume expanders, such as Dextran, should not be used. Fibrinogen and Dextran combine to form a complex, immobilizing about 10 per cent of the available fibrinogen.[11]

SUMMARY

An illustrative case report has been presented, accompanied by a brief review of the subject of amniotic fluid embolism, which is an entity usually characterized by respiratory distress, shock and a bleeding tendency. This patient demonstrated an uneventful antenatal course, a non-contributory medical history, prematurely ruptured membranes, a dead fetus with meconium present in the amniotic fluid, a hard labor, respiratory difficulty and shock in the delivery room, but no bleeding tendency was noted. There was a rapid progression of respiratory distress over the next two hours, and the clinical status rapidly worsened. There was no preceding or subsequent evidence of heart disease, either valvular, congenital, or pericardial. There was no evidence of toxemia, and little evidence in favor of pulmonary embolism due to thrombus, placenta, decidua or air. Idiopathic and Fiedler's myocarditis were unlikely, and the course was not typical of what one would expect with aspiration pneumonitis.

It is our feeling that this patient sustained an amniotic fluid embolism, and that she had either no fibrinogenopenia, or one of such mild degree, that further progres-

sion was suppressed by the steroids, antihistamines and plasma. Because of the anaphylactoid nature of this condition, it would appear that antihistamines and steroids are life-saving, and we strongly urge their usage in conjunction with the other therapy described in this paper.

RESUMEN

Se presenta un caso ilustrativo con una breve revisión del tema de la embolia de líquido amniótico, afección caracterizada por trastornos respiratorios, shock y tendencia a la hemorragia. Esta enferma mostró una evolución prepartum sin nada de particular, las membranas se rompieron prematuramente, había feto muerto con meconio en el líquido amniótico, trabajo de parto difícil, trastornos respiratorios y shock en el cuarto de trabajo, pero no se notó tendencia hemorrágica. Hubo empeoramiento rápido de los trastornos respiratorios en las siguientes dos horas, así como empeoramiento clínico. No había evidencias previas ni las hubo posteriormente de enfermedad cardiaca, ya sea congénita, valvular o pericárdica.

No había tampoco evidencia de toxemia, y pequeña evidencia en favor de embolia debida trombo, placenta, decídula o aire.

La miocarditis idiopática así somo las de Fiedler, no eran verosímiles y la evolución no fué la que era de esperarse en una neumonía por aspiración.

Es nuestra impresión que esta enferma sufrió una embolia de líquido amniótico y que ella no tenía fibronogenopenia, o algo así de menor grado en tal manera que se suprimió por el uso de esteroides y de antihistamínicos.

Por la naturaleza anafilactoide de esta afección parecería que los antihistamínicos y los esteroides son los médicamente capaces de salvar la vida y por éso aconsejamos su uso de manera decidida asociándolos a las otras medidas que se sugieren en este trabajo.

RESUME

Les auteurs présentent une communication explicative, complétée par une brève revue de la question de l'embolie par liquide amniotique. Il s'agit d'une entité généralement caractérisée par une difficulté respiratoire intense, un état de choc et une tendance à l'hémorragie. Ce malade avait eu une grossesse normale, une histoire médicale banale, la rupture prématurée de membranes, un foetus mort avec présence de meconium dans le liquide amniotique, un travail pénible, une gêne respiratoire et un état de choc dans la salle de délivrance, mais on ne nota aucune tendance à l'hémorragie. Il y eut une progression rapide de la difficulté respiratoire pendant les deux heures qui suivirent et l'état clinique empira rapidement. Il n'y avait aucune manifestation antérieure ou postérieure d'affection cardiaque, soit valvulaire, congénitale ou péricardique. Il n'y eut aucune manifestation de toxémie, il y eut quelques éléments en faveur d'une embolie pulmonaire due à un thrombus, au placenta, à la caduque, ou à l'air. Une myocardite idiopathique, ou une myocardite de Fiedler étaient improbables, et l'évolution ne présentait pas les caractéristiques de la pneumonie par aspiration.

Les auteurs ont l'impression que cette malade a été atteinte d'une embolie par liquide amniotique et qu'il y ait eu chez elle soit une absence totale de fibrinogène, soit une si faible teneur que l'aggravation ultérieure en fut arrêtée par les stéroïdes ou les antihistamines. La nature anaphylactique de cet état évoque l'idée que les antihistamines et les stéroïdes sont indispensables, et nous insistons fortement sur la nécessité de leur emploi en association avec l'autre traitement décrit dans cet article.

ZUSAMMENFASSUNG

Vorlage einer anschaulichen Krankengeschichte in Verbindung mit einer kurzen Übersicht über das Thema der Embolie durch Amnionflüssigkeit; dies ist ein Krankheitsbild, das gewöhnlich gekennzeichnet ist durch Atemnot, Schock und Blutungsneigung. Diese Patientin bot einen unauffälligen Verlauf in der Zeit vor der Niederkunft, eine auch sonst belanglose Vorgeschichte, vorzeitigen Blasensprung, eine tote Frucht mit Anwesenheit von Meconium in der Amnionflüssigkeit, erschwerte Wehentätigkeit, Atemstörungen und ein Schock im Kreissaal, aber keine Blutungsneigung waren das sich bietende Bild. In den nächsten 2 Stunden verstärkte sich die Atemnot rapid, und der klinische Status verschlechterte sich ebenso. Es bot sich kein vorausgehender oder nachfolgender Anhalt für eine Herzerkrankung, sei es eine solche der Placenta, sei sie angeboren oder pericardial. Es bestand auch kein Anhaltspunkt für eine Toxemie und wenig Anhalt zugunsten einer Lungenembolie durch einen Thrombus, Placenta, Decidua oder Luft. Eine idiopathische und Fiedler'sche Myocarditis war unwahrscheinlich, und der Verlauf war nicht typisch, wie man ihn erwarten würde bei einer Aspiration-Pneumonie.

Es ist unsere Überzeugung, dass diese Kranke eine Embolie durch Amnionflüssigkeit erlitt, und dass sie entweder keine Fibrinogenopenie hatte oder eine solche von milden Ausmass, so dass eine weitere Verschlechterung durch die Steroide und Antihistaminia verhindert wurde. Wegen der anaphylaktischen Natur dieses Zustandes

dürften Antihistaminica und Steroide lebensrettend sein, und wir drängen sehr auf ihre Verwendung in Verbindung mit der übrigen in dieser Mitteilung beschriebenen Behandlung.

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The Helium Closed Circuit Method for Measuring the Functional Residual Capacity

R. J. DiSALVO, M.D.* and UNOJI GOTO, M.D.**
Cincinnati, Ohio

The measurement of pulmonary ventilation by determination of the vital capacity, with its timed components, and the maximal breathing capacity is relatively simple. The various methods for determination of lung volumes, however, are for the most part complex and subject to considerable causes of error.

The use of helium as a foreign gas for measuring the functional residual capacity was first reported in 1941 by Meneely and Kaltreider.[1] A closed-circuit system, similar to that described by McMichael[2] using hydrogen, was used. In a subsequent publication[3] these authors critically analyzed the method and compared it with other procedures. A principle disadvantage of the method pertained to the constant volume required in the circuit during rebreathing; this was accomplished by adding oxygen to the system as rapidly as it was consumed by the subject. It proved difficult in most instances to match accurately the subject's oxygen consumption, and rather complex correction factors were required for correcting volume changes.

Recently, Meneely, Ball, Kory, Roehm, Mabe and Kaltreider[4-6] have simplified the method considerably by employing a closed-circuit system in which the subject rebreathes a mixture of helium and oxygen in air. Oxygen is not added to the circuit during the rebreathing period, and changes in helium concentration are continuously measured by a thermal conductivity unit.

It is the purpose of this report to describe our experiences with the simplified method (with minor modifications), and to present the results obtained in normal and emphysematous men.

Methods

1. Apparatus. The system is essentially the same as described previously except that a motor blower was substituted for the internal valves to provide mixing and a pump was inserted to provide for shunting the gas stream through a water saturator and the helium analyzer. A schematic diagram of the circuit is shown in Figure 1. The dead space in a 9 liter spirometer† was reduced by filling the area under the soda-lime cannister with paraffin to the top of the breathing tubes. The internal valves were removed. A motor blower† mixes the gases; a small aerator pump§ shunts part of the gas stream at a rate of 1.2 liters per minute through a water saturator and the thermal conductivity unit (helium

From the Veterans Administration Hospital, and the Department of Internal Medicine, University of Cincinnati College of Medicine.
*Assistant Clinical Professor of Medicine, University of Cincinnati College of Medicine; Chief, Cardiopulmonary Section, Veterans Administration Hospital.
**Fellow in Cardiopulmonary Diseases, Veterans Administration Hospital.
†Manufactured by Warren E. Collins Co., Boston, Mass.
§Gow-Mac Instrument Co.

katharometer),‡ and returns the gas downstream. Helium enters the katharometer cells by diffusion; errors due to "flow" do not occur provided the flow-rate through the unit is less than two liters per minute. The concentration of helium is read in absolute units from an indicating meter furnished with the unit.

2. Procedure. The dead space of the circuit was measured as follows: with the mouthpiece valve open to room air, the spirometer bell was pushed down to empty the circuit as completely as possible; the valve opening was then closed with a tight rubber stopper. Free mixing in the breathing tubes could then occur. A short "zero line" was inscribed on the kymograph paper, and 600-700 ml of helium admitted through the stopcock. The exact amount of helium added was determined by measuring the length of the vertical line caused by the movement of the bell to the nearest 0.1 mm. This figure was then multiplied by the bell factor (20.73 ml/mm.). The blower was turned on, and when the helium and dead space air were completely mixed, as indicated by a steady reading on the meter, the helium concentration was recorded.

Calculations were as follows:

$$\text{Dead space} = \left(\frac{\text{Amount of helium added}}{\text{Final helium concentration}}\right) - \text{helium added}$$

The mean of ten successive determinations of the dead space was 5630 ml. with a standard deviation of only 11.4 ml.

The accuracy of the meter was checked by connecting the circuit at the

‡Cambridge Instrument Co.

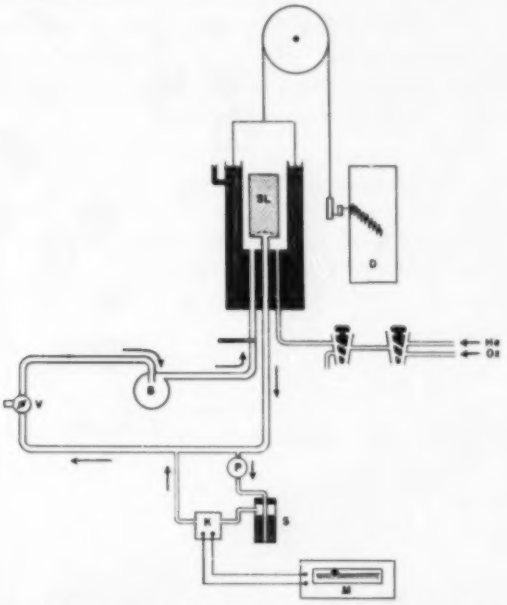

FIGURE 1: Schematic diagram of the circuit employed. The respirometer has a capacity of nine liters, and the internal valves have been removed. Helium and oxygen are admitted through the two stopcocks. SL, soda-lime CO_2 absorber; D, kymograph drum; B, motor blower; V, valve at which subject is connected by a rubber mouthpiece; P, aerator pump; S, water saturator; K, katharometer block containing the thermal conductivity unit; M, helium indicating meter.

mouthpiece valve to a small spirometer in which a dead space of 4000 ml. had been accurately measured with water. Helium was then added to the circuit, and the contents mixed by pumping the spirometer bells. The dead space of the spirometer measured with helium was 4005, 4018, and 4010 ml. on three consecutive determinations.

For measurement of the the functional residual capacity (FRC), the spirometer circuit is emptied; the mouthpiece valve is left in the open position and a tight rubber stopper inserted. A short "zero line" is inscribed and 1.0 to 1.5 liters of helium admitted (the larger amount when a high FRC is expected). A helium line is then drawn by gently turning the drum, the length of this line being such that it remains visible for 8 to 10 minutes with the drum revolving at slow speed (32 mm/min.). The drum is returned to the starting point, and 1.5 to 2.0 liters of oxygen admitted (Figure 2). The blower and aerator pump are turned on; the helium concentration, which is usually in the range of 13 to 14 per cent, is read from the indicating meter when constant readings are observed.

The mouthpiece valve is quickly snapped to the closed position, the stopper removed, and a mouthpiece attached. The subject is then connected and breathes room air until the respirations are quiet and stable; the drum is started at slow speed, and at the end of a normal expiration, the valve is turned and the subject connected to the circuit.

During the rebreathing period changes in helium concentration are read from the meter at one minute intervals (the amperage is checked before each reading), and a final reading taken when the respiratory base line crosses the helium line. The helium concentration at this moment depends on the amount of helium originally present, the dead space in the circuit, and the amount of air present in the subject's lungs at the time rebreathing of the helium mixture began. The calculation for the FRC is:

$$\text{FRC} = \left(\frac{\text{He added}}{\text{Final He Concentration}}\right) - (\text{He added} + \text{Dead Space} + \text{Correction Factor})$$

The correction factor is assumed to have a constant value of 200 ml., and is derived as follows[5]: a) 100 ml. for a small amount of helium absorbed (15 ml.); b) 30 ml. for change in the respiratory quotient; and, c) 70 ml. for an average nitrogen increment in the circuit of 3 per cent higher than room air. The latter correction is necessary since the thermal

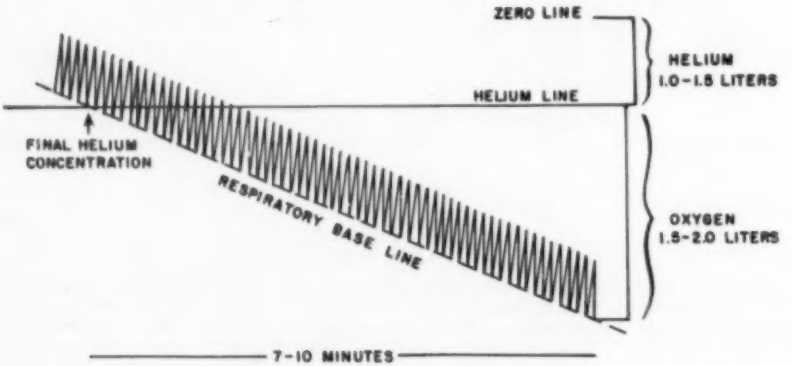

FIGURE 2: Explanation in text.

unit is calibrated for helium in air, and is slightly sensitive to nitrogen. The nitrogen concentration in the circuit immediately after the rebreathing period was measured in several instances with a nitrogen meter in normal and emphysematous subjects and found to vary between 2 and 5 per cent higher than room air.

The one minute meter readings are plotted as helium concentration against time, for evaluation of intrapulmonary gas mixing.

The FRC was measured in the sitting position in ten normal men, age range 26 to 43 years, mean 32 years and in 44 emphysematous subjects, age range 27 to 67 years, mean 52 years. Determinations were repeated at intervals of 20 to 30 minutes, and were required to check within 5 per cent. The vital capacity, inspiratory capacity, expiratory reserve volume, and maximal breathing capacity were determined with the same apparatus after removal of the soda-lime cannister. All values were corrected to body temperature and ambient barometric pressure, saturated with water vapor.[7] Arterial blood studies were performed by standard methods with the Van Slyke Apparatus;[8] pH was measured directly with a Cambridge Research Model pH Meter.

Results

The mean functional residual capacity in 10 normal subjects was 2.90 liters with a standard deviation of 0.75 liters. Additional data on these subjects, and comparison with results obtained by Hickam, Blair and Frayser[9] in normal men with their helium open-circuit method are presented in Table I.

In the subjects with emphysema, the FRC ranged from 2.80 liters to

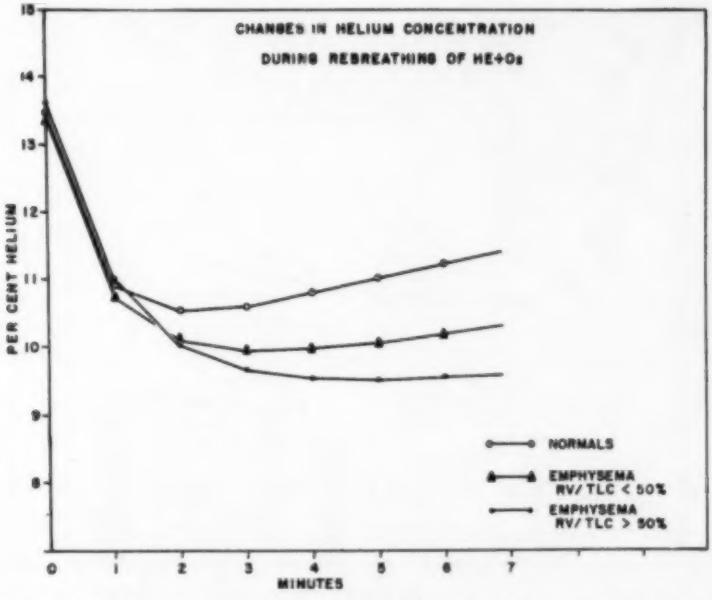

FIGURE 3: The curves represent the mean values for 10 normal subjects, fifteen patients with emphysema and RV/TLC ratios less than 50 per cent, and twenty-one emphysematous patients with ratios greater than 50 per cent.

TABLE I

	A	B
Number of Subjects	10	15
Age in years	32 ± 5.7*	25.3 ± 2.6
Surface area (M^2)	1.91 ± .17	1.92 ± .14
Vital capacity, liters	4.70 ± .66	4.80 ± .70
FRC, liters	2.90 ± .75	3.03 ± .37
Total lung capacity (TLC), liters	6.16 ± 1.11	6.16 ± .60
Residual volume (RV), liters	1.41 ± .45	1.37 ± .34
RV/TLC x 100	22.0 ± 1.38	22.3 ± 6.0

In column A are the data from the normal subjects in the present report. In column B are the values obtained by Hickam, Blair and Frayser[5] in normal seated men; the FRC was measured with an open-circuit helium method.

*Standard deviation.

8.2 liters, with a mean of 4.6 liters. For purposes of assessing relative severity, 36 patients in whom minute-to-minute changes in helium concentration were recorded were divided into two groups, depending on whether the ratio of the residual volume (RV) to the total lung capacity (TLC) was greater or less than 50 per cent. In Figure 3 are shown the mean values for the minute-to-minute changes in helium concentration during the rebreathing period in these two groups, as well as the mean values obtained in the normals. In the normals, the helium concentration began to rise between the second and third minute; a considerable difference is apparent in the curves obtained in the patients with emphysema.

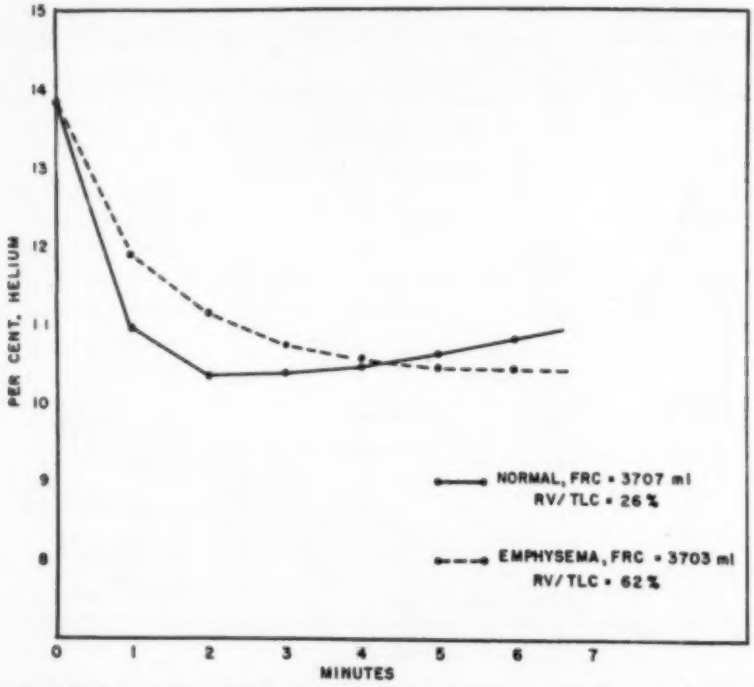

FIGURE 4: Comparison of helium mixing curves in a normal and an emphysematous subject with similar FRC values.

The concentration of helium fell to lower values, and in the more severe group continued to fall until the fifth or sixth minute. Figure 4 shows the curves from a normal and an emphysematous subject with identical functional residual capacities, and similar minute volumes.

In the emphysematous subjects, the RV/TLC ratios as determined from the FRC were correlated with the vital capacity, maximal breathing capacity, and per cent arterial oxygen saturation at rest. The results are shown in Figure 5.

Discussion

The simplicity of the method described in this report, and the rapidity with which determinations may be made offer several advantages over other procedures. The equipment required is not unduly expensive, and technical help is not required for the analysis of gas samples. The difficulty of obtaining representative alveolar gas samples in the nitrogen open-circuit method has been stressed repeatedly; alveolar gas samples are not required in the present method. It is likely that helium, because of its high diffusability, gives more accurate values for intrapulmonary gas mixing and the FRC than do methods based on changes in nitrogen or oxygen concentrations.[10]

The minute-to-minute changes in helium concentration which occur during the rebreathing period show an excellent correlation with the severity of the lung disease. Although intrapulmonary gas mixing evaluated in this manner is undoubtedly not as sensitive as that reported with the open-circuit helium procedure,[11] it is sufficiently accurate for routine clinical use, and may serve as a qualitative guide for the presence of defective mixing.

The reproducibility of the method, and the problem of the "oxygen storage" effect which results from rebreathing a mixture in which oxygen concentration constantly decreases have been comprehensively analyzed by Meneely, Ball, Kory, Roehm, Mabe and Kaltreider.[5, 6] In 42 serial duplicate determinations the standard deviation for all values of the FRC was ±121 ml.; the standard error of a pair was less than ±86 ml. in 95 per cent of instances. According to these authors, the error introduced by the oxygen storage effect is insignificant, and attempts to correct for it may result in even larger errors.

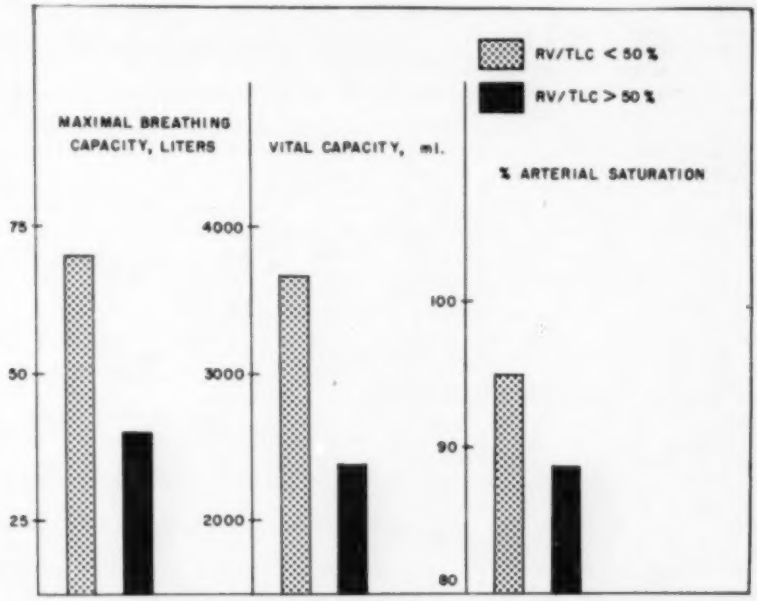

FIGURE 5: Comparative data between the lung volumes as obtained with the helium method and other tests of pulmonary function in the patients with emphysema. The bars represent mean values obtained from the same patients whose mixing curves are shown in Figure 3.

SUMMARY

1. The simplified helium method for measuring the FRC is described and results obtained in normal and emphysematous subjects are presented.
2. Minute-to-minute changes in helium concentration during the rebreathing period may be plotted against time to represent qualitative changes in intrapulmonary gas mixing. These curves correlate well with the severity of the emphysema.
3. The method is sufficiently accurate for routine clinical use.

RESUMEN

1. Se describe un método simplificado de helio para medir el FCR y también los resultados obtenidos en sujetos normales y enfisematosos.
2. Cambios minuto a minuto en la concentración de helio durante el período de respiración a circuito cerrado, pueden planearse en relación al tiempo para representar los cambios cualitativos en las mezclas de gases intrapulmonares. Estas curvas están en correlación con la severidad del enfisema.
3. El método es sufficientemente exacto para el uso clínico de rutina.

RESUME

1. L'auteur décrit la méthode simplifiée à l'hélium pour mesurer le FRC et les résultats obtenus chez des sujets normaux et emphysémateux.
2. Les modifications de minute en minute de la concentration de l'hélium pendant la période de reprise de la respiration peuvent être calculées en temps pour représenter les altérations qualitatives dans le mélange des gaz intrapulmonaire. Ces courbes correspondent bien à la gravité de l'emphysème.
3. La méthode est suffisamment précise pour l'emploi clinique courant.

ZUSAMMENFASSUNG

1. Beschreibung der vereinfachten Helium-Methode zur Mittlung der FRC und Vorweisung der bei normalen und emphysematösen Personen erzielten Ergebnissen.
2. Die von Minute zu Minute veränderte Heliumkonzentration im Verlauf der Rückatmungsperiode kann nach der Zeit kurvenmässig dargestellt werden, um qualitative Veränderungen des intrapulmonalen Gasaustausches zu beschreiben. Diese Kurven stimmen gut mit der Schwere des Emphysems überein.
3. Das Verfahren ist ausreichend genau für den routinemässigen klinischen Gebrauch.

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SECTION ON CARDIOVASCULAR DISEASES

The Use of an Artificial Foraminal Valve Prosthesis in the Closure of Interatrial and Interventricular Septal Defects

RAMON LARIOS, M.D., F.C.C.P.,* EDWARD A. FITCH, M.D.,**
GUMERSINDO BLANCO, M.D.† and CHARLES P. BAILEY, M.D., F.C.C.P.‡
Philadelphia, Pennsylvania

Closure of interatrial and interventricular septal defects has been practiced for some time[1] with generally rewarding results. Those employing direct vision techniques with extracorporeal circulation and artificial oxygenation have obtained complete closure of these communications by direct suture of the edge or by implantation of an Ivalon "patch." A satisfactory outcome may be expected in the majority of cases with this method. A significant number of patients remain, however, among whom postoperative difficulties and even deaths have resulted from the sudden alteration of hemodynamics[4] following the procedure. These alterations are associated with abrupt increase in the pressures within one or more of the heart chambers and concomitant failure of the myocardium in the face of the resulting overload. Such a situation is especially prone to develop after closure of defects associated with large shunts.

Ideally, such a defect should be closed gradually so that the right or left ventricle may adjust slowly to the altered circulation. Allowance should be provided for an escape vent during the early postoperative period so that a sudden increase of pressure within a chamber may be prevented.

To this end we have devised a prosthesis of our own design which allows unidirectional flow due to its flap valve construction and yet permits healing with eventual closure of the defect after a reasonably short period of time. Its action resembles that of the valve of the foramen ovale and we have felt justified in naming it an artificial foraminal valve prosthesis.

The prosthesis (Fig. 1) consists of a compressed ring of polyvinyl sponge (Ivalon*) intimately fused to a 90 degree arc of a semiflexible

*Former Fellow in Thoracic Surgery, Bailey Thoracic Clinic.
**Chief Resident in Thoracic Surgery, Hahnemann Medical College and Hospital and Bailey Thoracic Clinic; Public Health Service Research Fellow, National Heart Institute.
†Research Associate, Cardiac Surgery, Mary Bailey Foundation for Heart and Great Vessel Research.
‡Former Professor and Head, Department of Thoracic Surgery, Hahnemann Medical College and Hospital; Director, Bailey Thoracic Clinic.
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*Obtainable from Clay-Adams, Inc., New York, New York.

compressed sheet of the same material which is shaped to form a cover over the hole in the ring. The "ring" portion is sutured to the edge of the defect, and the "cover" portion is allowed to swing in one direction only.

The optimum compression for such a valve designed to be placed in an atrial septal defect, is seven to nine fold. The substance so compressed should maintain its contour in this relatively low-pressure area. However, it has been shown[3] that Ivalon is not a reliable material for use in areas of high pressure, especially when it is of pulsatile character (such as in aventricular septal defect). Aneurysmal dilatation, deterioration, and eventful fragmentation of Ivalon arterial grafts contraindicate their use for this purpose. Similar traumatic pressure effects surely must occur to any prosthesis implanted in an interventricular position.

However, by incorporating a stronger fabric within the substance of the Ivalon, its admirable qualities have been retained, and the added strength forestalls deterioration. This reinforced Ivalon may be used for constructing a prosthesis to be placed across interventricular septal defects. The technical aspects of the manufacture of the plain and the reinforced prosthesis will be described.

Construction of Prosthesis

I. Plain Ivalon valve for interatrial septal defects: The plain valve is more desirable in this location because it is not necessary to compress the Ivalon more than seven to nine fold. This results in a more pliable prosthesis which is easier to suture into place, and whose flap is more responsive to alterations in the pressure differential between the two atria.

A two centimeter thick slab of Ivalon is thoroughly wet, and another similar slab is placed directly upon it. A sheet of thin, fine mesh nylon cloth is placed partway between the two, thus allowing a portion of the two Ivalon slabs to lie in contact while the remainder of the surfaces are separated by the interposed cloth. This is carefully placed in a simple compression device (Fig. 2), taking care to maintain the edge of the cloth in a straight line in such a way as to form a smooth "hinge" between the two slabs. This total thickness of four centimeters is then compressed to exactly four millimeters, and the entire device is autoclaved. The heat "fixes" the plastic in the compressed state and simultaneously fuses the two slabs of Ivalon over the area of direct mutual contact (Fig. 3). After autoclaving for 10 minutes, the device is dropped into cool

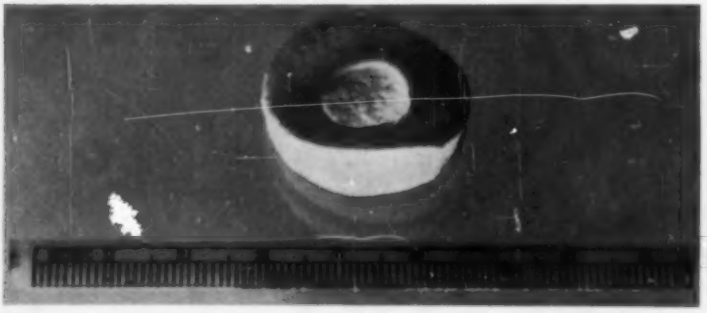

FIGURE 1: The completed prosthesis ready for implantation. The size of the hole is partially determined by the magnitude of the pre-existing shunt.

sterile water at the operating table. The wing nuts are released, the prosthesis is removed, and the nylon is discarded. The resultant partially fused compressed sheets then are easily trimmed and shaped to fit any septal defect, and the hole in the "ring" is placed as near to the fused "hinge" and made as large as seems appropriate for the particular case. When suturing the prosthesis in place, care should be taken to pass two or more stitches through both thicknesses in the hinge area to insure that the fused portions cannot become separated.

II. Reinforced valve for interventricular septal defects: The principle of manufacture is the same as above, with the exception that a Teflon netting* is incorporated within the substance of the "cover" portion of the valve. This is accomplished by selecting a three centimeter Ivalon slab and applying the nylon cloth partially over its surface. Next, a 1 centimeter slab is placed followed by a sheet of Teflon netting and finally by another 1 centimeter Ivalon slab. This "sandwich" is placed in the press and compressed to five millimeters. It is autoclaved and shaped as before. The resultant valve has a "ring" portion three millimeters thick with a two millimeters thick "cover." The "cover" has the strengthening Teflon fused within its substance.

*Obtainable from John Sidebotham, Inc., Philadelphia, Pennsylvania.

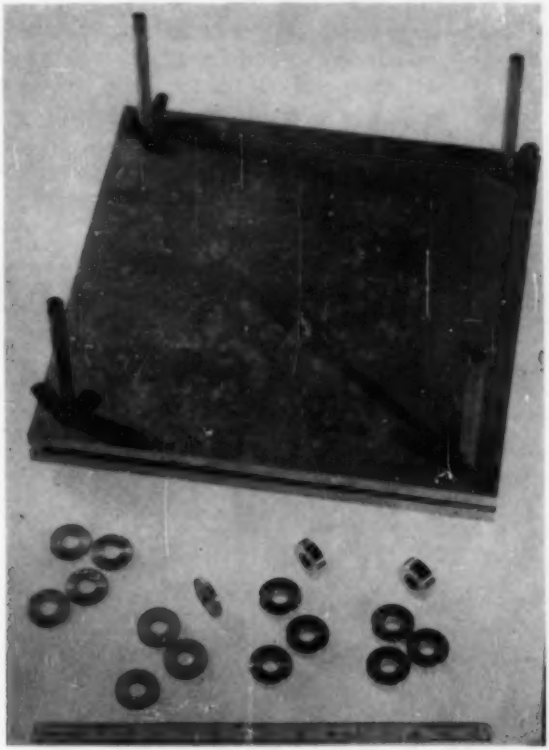

FIGURE 2: A simple two plate device is used to compress the commercial Ivalon. The desired thickness is achieved by separating washers of known thickness.

It is not necessary to reinforce the "ring," as it is only when the valve is shut that any great pressure differential is applied to the closed and strengthened "cover" portion.

Experimental Methods[2, 5, 6]

Adult mongrel dogs were utilized to work out the technical details of valve insertion. Intravenous sodium pentothal anesthesia, endotracheal intubation, and a mechanical respiration were utilized. Right thoracotomy was performed through the fifth intercostal space. The azygos vein was doubly ligated and divided. The superior and inferior vena cavae were isolated with tapes, and the pericardium incised. Preparations for extracorporeal circulation were made using a Kay-Cross rotating disk oxygenator and a Sigmamotor pump. The machine was turned on, the caval tapes tightened, and the aorta and pulmonary artery were cross clamped. No cardioplegic drugs were employed. The anterior right atrial wall was incised generously and a septal defect varying between 1.5 and 2.0 cm. in diameter was created in the region of the fossa ovalis. A previously prepared Ivalon foraminal valve prosthesis was inserted (Fig. 4). In one series, the flap was placed on the right and in the other on the left side of the septum. After suturing the valve prosthesis to the margin of the defect, the left atrial cavity was flooded with saline solution through the hole in the valve "ring" to evacuate any trapped air. The right atrium was likewise filled with saline and the atriotomy closed with a running suture. The heart was usually beating weakly or arrested at this point but upon release of the aortic and pulmonary cross clamp strong contractions resumed. If ventricular fibrillation appeared, an electric shock was applied. The chest incision was then closed in layers leaving a drainage tube in the right pleural cavity for suction drainage during the following two to four hours. Three hundred thousand units of procaine penicillin was given intramuscularly on the day of operation and for three successive days thereafter. The animals were sacrificed at intervals up to six weeks

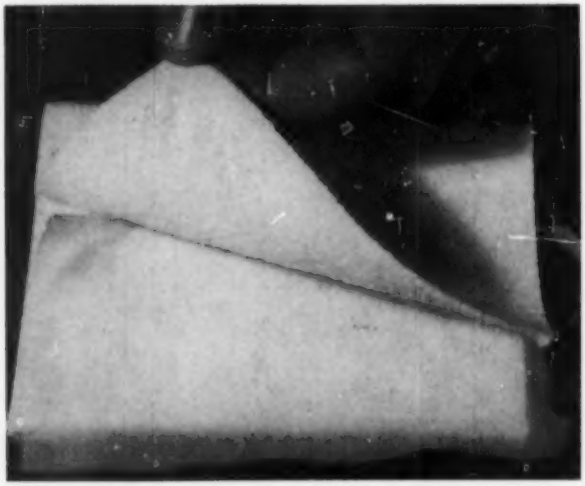

FIGURE 3: A sheet of nylon is used to prevent fusion of the two Ivalon slabs except at the hinged border.

after the operation and the atrial septum with its implanted prosthesis was examined grossly and histologically.

Results

Multiple microscopic sections taken through the region of implantation of the valve shows healing proceeding gradually from a few days after implantation (Fig. 5) to completion with closure of the defect about three to four weeks after operation (Fig. 6). The prosthesis becomes encased within a layer of fibroconnective tissue (Fig. 7) with minimal foreign body giant cell reaction. The foreign body reaction is largely limited to the area of the suture material. Granulation tissue is also found between the fixed (ring) and movable (cover) portions of the valve. Fibroblastic proliferation infiltrates the interstices of the Ivalon sponge. Thus the valve becomes closed by granulation and fibroconnective tissue and the whole prosthesis encased within a surrounding layer of mature fibroconnective tissue.

Clinical Experience

The prosthesis has been employed clinically in nine patients prior to submission of this paper with interatrial or interventricular septal defects, or the Tetralogy of Fallot (Fig. 8).

Case 1: A. S., a 50 year old white woman was admitted to the Hahnemann Hospital on October 22, 1957, with the chief complaint of shortness of breath on exertion of several years duration. She denied any history of rheumatic disease but admitted that a heart murmur had been discovered when she was hospitalized for hysterectomy

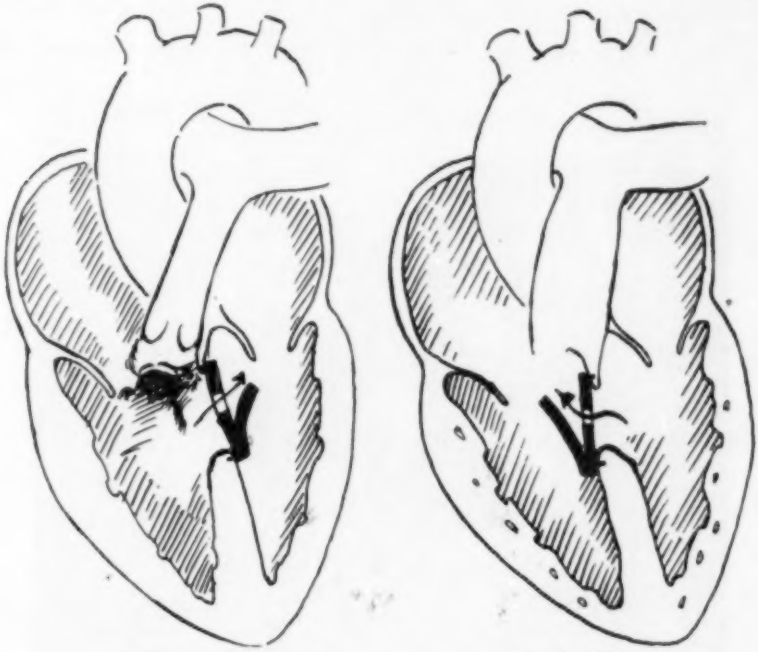

FIGURE 4A FIGURE 4B

Figure 4, A and *B:* Diagrammatic sequence showing the details of the experimental method of placing the artificial foraminal valve prosthesis.

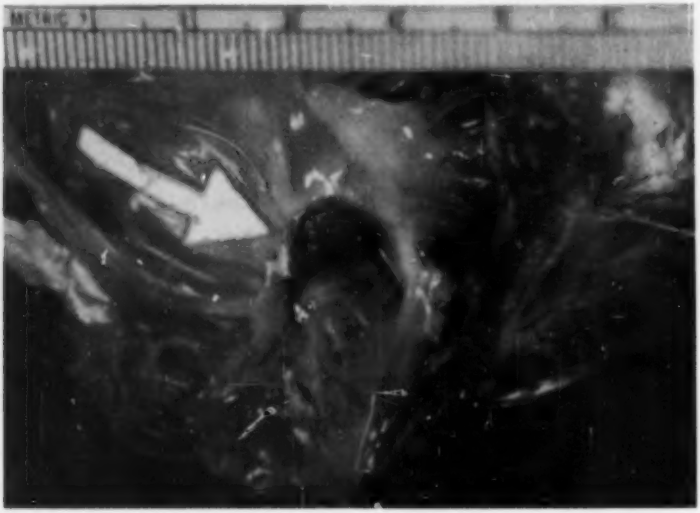

FIGURE 5: This dog was sacrificed at 48 hours. There is a small thrombus on the flap (within the ring hole) as seen from the left atrium.

in 1950. Physical examination showed a grade II to III harsh systolic murmur best heard at the left second and third interspaces accompanied by a grade I blowing diastolic murmur in the same area. The first mitral sound was accentuated, P2 was markedly accentuated and split. There were occasional premature ventricular contractions.

Roentgenograms showed 2 plus enlargement of the heart with prominent pulmonary and hilar vessels. There was 1 plus enlargement of the left atrium.

The electrocardiogram showed normal sinus rhythm and right ventricular hypertrophy.

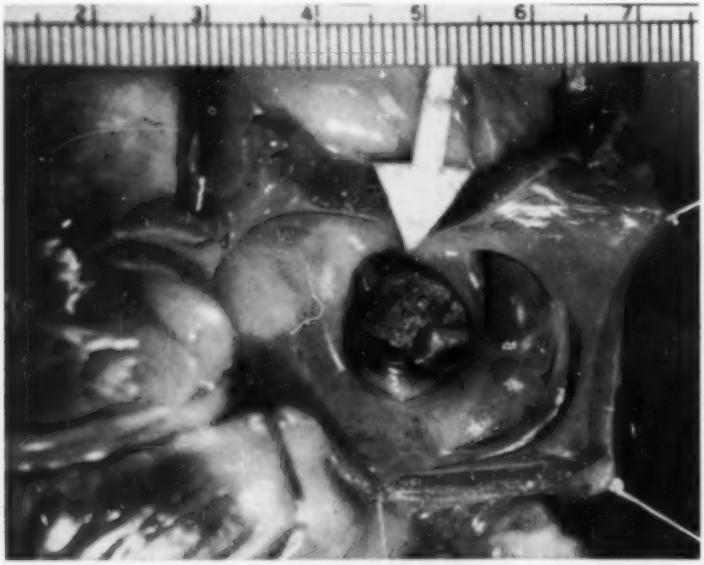

FIGURE 6: This prosthesis is shown six weeks after implantation. From the right atrial aspect, fibrous tissue is seen growing out over the valve flap, effectively preventing further shunting from the left atrial side.

Cardiac catheterization performed on October 23, 1957, showed an increase in oxygen content in the right atrial samples. There was systemic arterial oxygen unsaturation (89%). Pulmonary artery pressure was 63/19 mmHg. Right ventricular pressure was 64/1 mmHg.

The clinical diagnosis was atrial septal defect with moderately severe pulmonary hypertension.

Surgery was considered hazardous in view of the catheterization findings which suggested a balanced shunt with slight arterial oxygen unsaturation.

An operation for closure of the defect was advised, however, and performed on December 20, 1957, at which time closure of a 4 cm. ostium secundum defect in the interatrial septum was effected using total cardiopulmonary bypass. An artificial foraminal valve prosthesis which allowed a right-to-left but no left-to-right flow was inserted.

She tolerated the procedure well and after an uneventful recovery was discharged on January 8, 1958. Postoperative cardiac catheterization done on January 6, 1958, showed persistence of pulmonary hypertension with a right-to-left, but no left-to-right shunt. A second catheterization, July 25, 1958 revealed a small persistent bidirectional shunt and a reduction of the pulmonary artery pressure from 80 mmHg. to 40 mmHg.

Case 2: E. R., a three and one half year old white boy was admitted to Hahnemann Hospital on January 27, 1958, for evaluation of his cardiac status. A heart murmur had been discovered when he was 10 days old. Although his early development appeared normal, in the last few months the mother had noticed mild cyanosis after exertion. This was accompanied by obviously diminished exercise tolerance.

On physical examination, the pertinent findings included a prominence of the left precordium and a rough systolic murmur in the second and third interspaces.

Roentgenograms of the heart showed a 2 plus enlargement predominantly of the right ventricle.

The electrocardiogram showed marked right axis deviation and evidence of right ventricular hypertrophy.

Cardiac catheterization done on January 31, 1958, showed the right ventricular pressure to be 95/6 mmHg., and the pulmonary artery pressure to be 15/2 mmHg. During the procedure, the catheter was maneuvered into the aorta through a ventricular septal defect. The peripheral oxygen saturation was 76 per cent.

A diagnosis of the Tetralogy of Fallot was made and surgery advised.

On February 2, 1958, he was operated upon with the aid of a pump oxygenator. An infundibular obstruction was resected and the ventricular septal defect was closed with an artificial foraminal valve prosthesis which permitted a right-to-left shunt.

Postoperatively he did well. The systolic murmur heard over the second and third interspaces was much less intense than preoperatively. The pulmonic second sound was audible. He was discharged on February 19, 1958. No post-operative catheterization has been carried out.

Case 3: T. A., a 36 year old white woman was admitted to Hahnemann Hospital on February 10, 1958 with a chief complaint of fatigue and shortness of breath. In

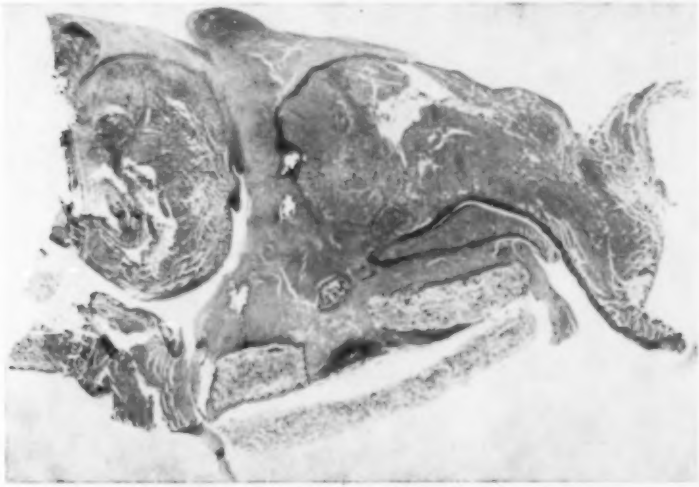

FIGURE 7: Photomicrograph showing the coaptation of the sealed valve, completely covered by host tissue on the ring side, and almost complete encasement on the flap side.

1935 during her fourth and last pregnancy she suffered from an episode of dyspnea and orthopnea, accompanied by peripheral edema. She received digitalis and was placed on bed rest. In the months just previous to this admission, the aforementioned symptoms had reappeared and increased in severity.

Physical examination showed a blowing systolic grade II murmur over the left third and fourth interspaces along the sternal border.

Roentgenograms showed 1 plus enlargement of the heart.

Right heart catheterization showed normal pressures within the right chambers and an increase in the oxygen content of the right atrial sample over that of the superior vena cava. There was a marked increase in pulmonary blood flow and a large left-to-right shunt. There was no peripheral arterial unsaturation. An atrial septal defect was suspected.

Operation was carried out on March 4, 1958 with the aid of a pump oxygenator. A large interatrial septal defect was repaired using an Ivalon artificial foraminal valve prosthesis placed in such a way as to allow left-to-right shunting.

She had an uneventful postoperative course. A second right heart catheterization performed on March 20, 1958 showed no evidence of an intracardiac shunt.

Case 4: V. T., a nine year old white boy was admitted to Hahnemann Hospital on March 4, 1958. His early development was normal. At six months of age a heart murmur was noticed. He was asymptomatic until age three when shortness of breath and squatting appeared on exertion. There was mild cyanosis, but no clubbing of the fingers, hemoptysis, or edema.

On physical examination, there was a harsh grade II systolic thrill over the third left interspace. A harsh grade II systolic murmur was heard over the same area.

Cardiac catheterization done on March 10, 1958 showed marked right ventricular

FIG. 8A

FIG. 8B

(*See Legend on Next Page*)

hypertension of 93/5 mm. Hg. with a pulmonary artery pressure of 13/5 mm. Hg. There was systemic arterial unsaturation. The diagnosis of Tetralogy of Fallot with a predominantly right-to-left shunt was made.

On March 18, 1958, a repair of the interventricular septal defect and correction of the pulmonic stenosis was undertaken. This was performed using an Ivalon artificial foraminal valve prosthesis allowing a right-to-left shunt. The pump oxygenator was used.

Twelve hours after the procedure he showed excessive bloody drainage from his left thorax. Roentgenograms showed a large collection of blood in the left hemithorax.

Reoperation was undertaken on March 19, 1958 and the clot evacuated. Bleeding was found to originate at the suture line in the right ventricle. As the bleeding site was being sutured, cardiac arrest occurred. Efforts at massage were temporarily successful but cardiac contraction weakened and disappeared eventually in spite of the use of an electric pacemaker.

Case 5: J. K., a four year old white girl was admitted to Hahnemann Hospital on February 13, 1958, with a history of frequent upper respiratory infections during the previous two years. A heart murmur had been discovered when she was two years old.

On examination, the left precordium was prominent and a thrill could be felt over the left third and fourth interspaces. A grade II to III rough systolic murmur could be heard over these interspaces in the parasternal area. The pulmonic second sound was split and loud.

Roentgenograms showed the cardiac enlargement to be predominantly of the right ventricle. The pulmonary artery segment was enlarged 2 plus.

Right heart catheterization performed on February 17, 1958 showed a right atrial pressure of 34 mm. Hg. The right ventricular pressure was 26/0 mm. Hg. and the pulmonary artery pressure 26/10 mm. Hg. The catheter could be maneuvered into the aorta through an interventricular septal defect. The oxygen data did not show evidence of a shunt.

At surgery, on April 19, 1958, a high interventricular septal defect was closed with a prosthetic foraminal valve permitting continuance of a left-to-right shunt. An incidental finding was the presence of an anomalous left superior vena cava draining into the coronary sinus.

The postoperative course was uneventful.

Recatheterization on May 2, 1958 showed no intracardiac shunt.

Case 6: L. B., a 20 months old white baby girl was admitted to Hahnemann Hospital on April 7, 1958 with a diagnosis of Tetralogy of Fallot. She was born with a heart murmur and had shown cyanosis, shortness of breath and squatting on exertion.

FIG. 8C

Figure 8, A, B and *C:* Clinical photographs showing a valve sutured in place so as to allow only a right to left shunt.

On physical examination she showed a grade III harsh systolic murmur over the precordium which was loudest at the left sternal border in the third interspace where it was accompanied by a thrill.

Cardiac catheterization showed an increase in the oxygen content of the right ventricular sample and marked right ventricular hypertension (R. V. = 93/3 mm. Hg., brachial artery 71/33 mm. Hg.). During the procedure the catheter appeared to pass from the right atrium into a pulmonary vein. A large right-to-left shunt was demonstrated. The pulmonary artery could not be entered.

At operation on April 22, 1958, a high interventricular septal defect was found in addition to an infundibular pulmonic stenosis. The latter was resected. The defect was closed with a foraminal valve prosthesis allowing a right-to-left flow.

The postoperative course was uneventful.

She was discharged on May 3, 1958. At this time the only significant finding was the presence of right bundle branch block. Cyanosis had disappeared completely. Postoperative catheterization was unsatisfactory for technical reasons.

Case 7: H. W., a 26 year old white man was admitted to Hahnemann Hospital on May 25, 1958 complaining of moderate cyanosis and mild dyspnea on exertion. A heart murmur had been detected when he was six months old.

On physical examination he showed mild cyanosis of fingernails and lips. There was a grade III rough systolic murmur heard all over the precordium but loudest over the third left interspace. The second pulmonic sound was absent and the second aortic sound was decreased in intensity.

Roentgenograms showed the heart size and configuration to be within normal limits.

During right heart catheterization the catheter could be advanced from the right ventricle into the aorta. Severe right ventricular hypertension existed. The catheter could not be advanced into the pulmonic artery. The data was indicative of interventricular septal defect, or Fallot's tetralogy.

On May 4, 1958 he was operated upon with the aid of a pump oxygenator. A diagnosis of Tetralogy of Fallot was established. The ventricular septal defect was closed with a foraminal valve prosthesis inserted in such a way as to permit flow from right to left. The infundibular obstruction was resected.

He recovered rapidly from this operation. When discharged on June 19, 1958, his condition was markedly improved. A postoperative right-heart catheterization on August 5, 1958 revealed an intracardiac pressure and oxygen value within normal limits.

Case 8: G. R., a 21 year old white man was admitted to Hahnemann Hospital on May 5, 1958 complaining of dyspnea on exertion and palpitations. He had had a heart murmur since birth.

On physical examination there was a grade II systolic murmur at the pulmonic area and at the apex.

Roentgenograms showed grade I-II right ventricular enlargement with enlargement of the pulmonary artery segment.

Cardiac catheterization on July 9, 1956 showed an increase in oxygen content of the right mid atrial sample and a slight right ventricle-pulmonary artery pressure gradient. The diagnosis was felt to be interatrial septal defect, possibly of the ostium primum type.

Left ventriculography showed evidence of some mitral regurgitation.

At operation on May 20, 1958 there were two interatrial septal defects which were converted into a common defect and closed with an artificial foraminal valve prosthesis allowing a left-to-right shunt.

Postoperatively, he did well and was discharged on June 6, 1958. Catheterization has not been repeated as yet.

Case 9: J. B., a 19 year old white man was admitted to Hahnemann Hospital on May 15, 1958, for evaluation of his cardiac status. Pertinent details in his past history revealed that he was a "blue baby" at birth and since then complained that he tires and becomes dyspenic upon slight exertion.

Physical examination revealed a prominent left precordium, enlargement of the heart to the left and a faint systolic thrill over the left fourth interspace near the sternal border and transmitted over the entire chest. An early diastolic blowing murmur was best heard over this same area.

On x-ray examination, the pulmonary artery segment was dilated and the heart showed two plus enlargement.

Right heart catheterization revealed a gradient of 70 mm. Hg. across the pulmonic valve and an oxygen step up in the right ventricle. These findings were suggestive of a ventricular septal defect and pulmonic stenosis.

On June 11, 1958 he was operated upon with the aid of a pump oxygenator. A large interventricular septal defect was closed with a foraminal valve prosthesis. A hypertrophied infundibular ridge was excised.

The postoperative course was uneventful except for accumulations of pericardial fluid which necessitated repeated tappings. He was discharged improved on July 8, 1958. As yet, the catheterization has not been repeated.

Comment

In these patients an artificial foraminal valve prosthesis made of Ivalon has been implanted in interatrial or interventricular communications instead of using the more conventional methods of closure. This valve is designed to provide a temporary vent between the heart chambers and thus to protect them from the sudden increases in intracardiac pressures which may attend complete closure of such defects. We have obtained laboratory evidence showing that the valve affords a mechanism whereby healing across the defect takes place gradually over a period of several weeks.

SUMMARY

A direct method of closure of interatrial or interventricular septal defects employing an artificial foraminal valve made of compressed Ivalon is described.

Experimental studies are presented which show the healing process to result in complete closure of defects within three weeks of implantation.

Our early clinical experiences with such a prosthesis has been presented. It is no harder to apply than is a simple Ivalon patch.

RESUMEN

Se describe un método directo de clausura interatrial o interventricular de los defectos del tabique, empleando una válvula de Ivalon comprimido para la oclusión del foramen.

Se presentan estudios experimentales que muestran el proceso curativo obteniéndose el cierre completo del defecto dentro de tres semanas después de su implantación.

Nuestras experiencias clínicas con tal prótesis se presentan. No es más difícil de aplicar que un parche simple de Ivalon.

RESUME

Les auteurs décrivent une méthode directe de fermeture des défauts de la paroi inter-auriculaire ou interventriculaire, par une valvule perforée artificielle, en Ivalon comprimé.

Ils présentent des études expérimentales qui montreat le processus de guérison amenant à la fermeture complète des défauts en trois semaines d'implantation.

L'expérience clinique récente des auteurs avec une telle prothèse est présentée. Elle n'est pas d'une application plus difficile que celle d'une simple plaque d'Ivalon.

ZUSAMMENFASSUNG

Beschreibung einer direkten Methode des Verschlusses eines Vorhof- oder Kammer-Scheidewand-Defektes unter Verwendung einer künstlichen, gelochten Klappe aus komprimiertem Ivalon.

Wiedergabe experimenteller Untersuchungen, die den Heilungsprozess zeigen, der mit einem kompletten Verschluss des Defektes innerhalb von 3 Wochen nach der Implantation endet.

Unsere ersten klinischen Erfahrungen mit einer solchen Prothese werden vorgelegt; sie ist nicht schwieriger zu handhaben als ein gewöhnlicher Ivalon-Lappen.

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Angiocardiography with Hypaque-M, 90 Per Cent*

WILLIAM T. MESZAROS, M.D.,** WILLIAM B. BUCKINGHAM, M.D., F.C.C.P.,***
GEORGE C. SUTTON, M.D.† and GEORGE W. HOLMES, M.D., F.C.C.P.‡
Chicago, Illinois

The ideal angiocardiographic contrast medium should be capable of producing good visualization of both right and left cardiac chambers and great vessels, and should be free of serious toxic reactions. The quality of the radiograms is determined by the x-ray equipment, the site and speed of the injection, and the type and concentration of contrast material.

In children, the amount injected is proportioned to the weight of the child, and usually both right and left cardiac chambers are readily visualized. In adults, demonstration of the right heart chambers is usually successful. However, visualization of the left cardiac chambers and aorta remains a difficult problem in adults. The present high level of modern thoracic surgery creates a need for more accurate angiocardiographic diagnosis. This need has been partially met by improved x-ray apparatus and rapid film-changing devices.[1] The introduction of intra-cardiac or central injection of the contrast medium has resulted in a higher concentration of dye reaching the left heart and therefore better definition of these chambers.[2] The recently introduced 90 per cent Hypaque has been reported to produce good radiological contrast and few reactions.[3] The Hypaque referred to in this study is Hypaque-M, 90 per cent, a mixture of the sodium and n-methylglucamine salts of diatrizoic acid.

This is a report of 105 consecutive angiocardiograms using 90 per cent Hypaque performed at the Cook County Hospital. The study included 67 adults and 38 children.

Procedure

All angiocardiograms were performed and viewed by one team of physicians. A standard Robb-Steinberg needle and rapid emptying 50 cc. syringe were used for peripheral injections. The injection was accomplished as quickly as possible, usually in less than three seconds. Intracardiac injections were accomplished through a Lehman catheter of the largest possible diameter. A manual lever type pump was used to rapidly inject the 90 per cent Hypaque. The tip of the catheter was placed in the right atrium, right ventricle, or pulmonary artery, depending upon which structures were to be visualized. In all cases labeled "intracardiac injection" the catheter was in the right atrium or beyond.

An Elema biplane film changer was used, with two radiographic tubes. The usual exposure factors were 300 milliamperes, 1/60 or 1/30 second, and kilovolts up to 125. Exposure rate varied from one to eight per second.

Simultaneous anterior-posterior and lateral views were taken for approximately 20 seconds after injection. Occasionally the patient was positioned to obtain simultaneous right and left oblique views. The majority

*From Cook County Hospital.
**Director, Diagnostic Radiology.
***Associate Attending Physician.
†Associate Attending Physician.
‡Chief, Thoracic Surgery.

of the adult peripheral injections was performed with the patient seated, with the arm raised above the head. All central injections were performed with the patient recumbent.

The pathological diagnoses in the adult cases were varied, including both cardiac and pulmonary diseases. These patients were predominantly male (60 per cent), with ages up to 89 years. The amount of Hypaque used in adults was usually 50 cc. In 12 cases more (from 60 to 80 cc.) was injected, and in six cases less (20 to 35 cc.). The site of injection was peripheral in 34 and central in 33 cases.

Peripheral angiocardiography was performed in the infants, all with various types of congenital heart disease. The amount injected was 2 cc. per kilogram. The youngest infant in the series was one month of age.

Reactions

There were no fatal or serious reactions in the entire series. Indeed, most patients had no reaction whatsoever to 90 per cent Hypaque. A slight sense of heat was noted by 18 patients and coughing occurred in 5. Vomiting, nausea, headache, and insulin reaction were noted in one patient each. There was no relation between dosage of Hypaque and observed reactions. One child developed a single urticarial wheal, which lasted 24 hours. The total incidence of mild reactions was 26.6 per cent.

TABLE I—ANALYSIS OF SEVENTEEN CASES OF INADEQUATE LEFT SIDED VISUALIZATION IN ADULTS

Diagnosis	Site of Injection	Amount	Reason for Failure
1. Aortic aneurysm	Central	25 cc.	A slow injection of small amount of dye through a Cournand Catheter
2. Tumor of lung	Peripheral	50 cc.	Superior vena cava completely obstructed
3. Aortic aneurysm	Central	50 cc.	Unknown
4. Tumor of lung	Peripheral	25 cc.	Vena Cava completely obstructed
5. Tumor of lung	Peripheral	50 cc.	Vena cava completely obstructed
6. Pneumoconiosis	Central	50 cc.	Unknown
7. Mitral stenosis	Central	75 cc.	Large left atrium impeded further passage of dye
8. Tuberculosis	Central	20 cc.	Small amount of dye
9. Patent Ductus	Central	60 cc.	Unknown
10. Mediastinal tumor	Peripheral	50 cc.	Unknown
11. Mediastinal tumor	Peripheral	50 cc.	Unknown
12. Arteriosclerotic H.D.	Central	25 cc.	Small amount of dye
13. Arteriosclerotic H.D.	Peripheral	50 cc.	Unknown
14. Left pleural effusion	Central	50 cc.	Unknown
15. Mediastinal tumor	Central	50 cc.	Slow injection
16. Mediastinal tumor	Peripheral	50 cc.	Superior mediastinal obstruction
17. Pericarditis	Peripheral	50 cc.	Unknown
SUMMARY:	8-Peripheral 9-Central	25-75 cc.	Pathological Reasons (5) Technical Reasons (4) No reason (8)

Visualization

The angiocardiograms were of excellent diagnostic quality in all pediatric cases.

When injected, the right heart and pulmonary vasculature were well seen in all adults. Adequate visualization of the left heart and aorta occurred with equal frequency with either site of injection. However, clearer detail and sharper contrast of the left sided structures were observed with successful central injection.

In 17 of the cases visualization of the left heart was inadequate. Detailed analysis of these 17 cases is given in Table I. The failure was not influenced by the site of injection, since nine were central and eight were peripheral. Five of this group of failures were unavoidable because of the nature of the pathology, and in four there was a frank technical error. No reason for inadequate visualization was apparent in 8 cases. This represents the low percentage of failure (12 per cent) inherent in this procedure.

Discussion

Hypaque-M, 90 per cent is a solution of high density and therefore serves well as a contrast medium for angiocardiography. In the analysis of results of the present series, this medium was of particular value in levo-angiocardiography of adults. Diagnostic visualization of the left heart and aorta was achieved in the majority of patients without the need for central intra-cardiac injection. Regardless of the site of injection, the substance produced only mild infrequent reactions in both adults and children. Thus, in regard to the radiological contrast and clinical toxicity, excellent results were obtained in this study of 105 patients.

Case Reports

The following cases illustrate the quality of visualization and the diagnostic information obtained with 90 per cent Hypaque:

Case 1: J. G., white man, age 55, had noticed chest pain for the previous 10 months. Roentgen study revealed a mass in the left upper chest. He was referred to the hospital for further study.

Physical examination was essentially negative. Serologic tests for syphilis were strongly positive.

Angiocardiography revealed the mass to opacify, confirming the diagnosis of aortic aneurysm.

At surgery, an aneurysm was found.

Case 2: B. W., Negress, age 60, was admitted to Cook County Hospital because of

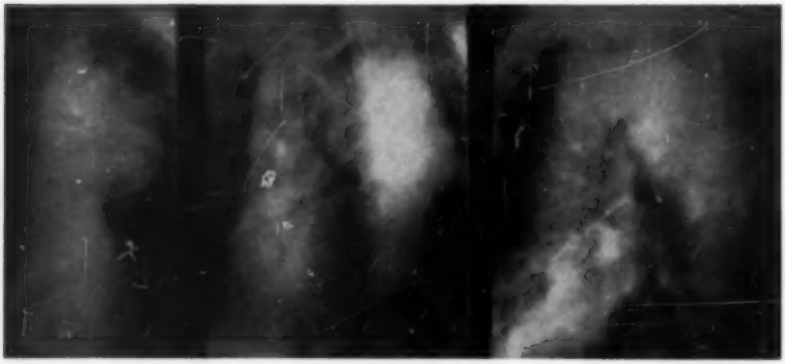

FIGURE 1 (Case 1): Left and center: Preliminary films. Posterior left mediastinal mass. Trachea is deviated to the right and anteriorly. Right: Angiocardiogram, 11 seconds after injection into antecubital vein. Opacification of aorta and large aneurysm of posterior portion of aortic arch and upper portion of thoracic aorta.

FIGURE 2

FIGURE 3

Figure 2 (Case 2): Eight seconds after injection into antecubital vein. Opacification of large aortic arch aneurysm and descending aorta. Non-opacified mass adjacent to aneurysm is encapsulated hemothorax which followed previous rupture of aneurysm.—*Figure 3* (Case 2): Lateral view at eight seconds. The aneurysm is clearly outlined. A.A.—ascending aorta; P.A.—pulmonary artery; AN—aneurysm; D.A.—descending aorta.

fever and chills for two weeks. She complained of weakness and pain in the left chest when coughing.

Physical examination revealed dullness in the left chest, with absent breath sounds. Wassermann and Kahn tests were positive.

Bronchoscopy revealed a left endobronchitis. The left vocal cord was paralyzed. Scalene node biopsy was negative. Left thoracentesis revealed grossly bloody fluid.

Roentgen examination on admission showed a massive left pleural effusion. Follow-up film post-thoracentesis revealed a large mass in the left upper chest. On fluoroscopic examination pulsation was noted. Angiocardiography revealed a large aneurysm of the aortic arch. Surrounding the aneurysm was a homogeneous density interpreted as encapsulated hemothorax.

At surgery, the diagnosis of a large aneurysm of the aortic arch was confirmed.

Case 3: L. S., a Negress, age 52, entered the hospital with fever and weakness. Dyspnea on exertion and cough had been present for eight months.

FIGURE 4 (Case 3): Left: Preliminary film. Right superior mediastinal mass, with calcific outer border. Also: left ventricular enlargement, large sclerotic aorta, and resolving pneumonitis, left lung. Center: Angiocardiogram at 13 seconds. Opacification of aneurysm of innominate artery. Double arrows: lateral margin of contrast material. Region between single and double arrows represents non-opacified thrombus. Right: Lateral view. Aneurysmal dilatation of both ascending aorta and innominate artery is noted.

Physical examination revealed signs of consolidation in the left chest. Blood pressure was 164/85. Pulses were equal in both arms. There was a soft, grade II basal systolic murmur.

Kahn test was negative. Wassermann test was anticomplementary.

Roentgen examination of the chest showed an area of pneumonitis in the left lung. The heart was enlarged, with prominence of the left ventricle. A large mass was noted in the right superior mediastinum. There was a marginal rim of calcification about the mass.

Angiocardiography revealed aneurysmal dilatation of the ascending aorta and innominate artery. A thrombus in the innominate artery was clearly demonstrated.

Case 4: E. M., a white woman, age 72, was admitted to the hospital in 1957 for study of a mass in the chest. This had been discovered on a routine chest survey film in 1953. Follow-up film in 1954 showed a 100 per cent increase in size. Examinations in 1956 and 1957 showed further enlargement of this mass.

She was asymptomatic. Physical findings were essentially negative.

Roentgen examination revealed a large mass mainly in the right anterior mediastinum, the posterior border of which extended into the middle mediastinum. One observer believed the mass to pulsate, although this was thought to be transmitted, rather than intrinsic.

On angiocardiography the heart and great vessels were not related to the mass, indicating that the mass was extravascular.

Surgery was not performed. Final clinical diagnosis was probable bronchogenic cyst.

Case 5: E. C., Negress, age 36, entered the hospital because of low back pain. A mass in the chest was discovered as an incidental finding.

On careful questioning, she gave a history of intermittent fullness in the left anterior chest, at the level of the sternoclavicular junction. There was occasional minimal

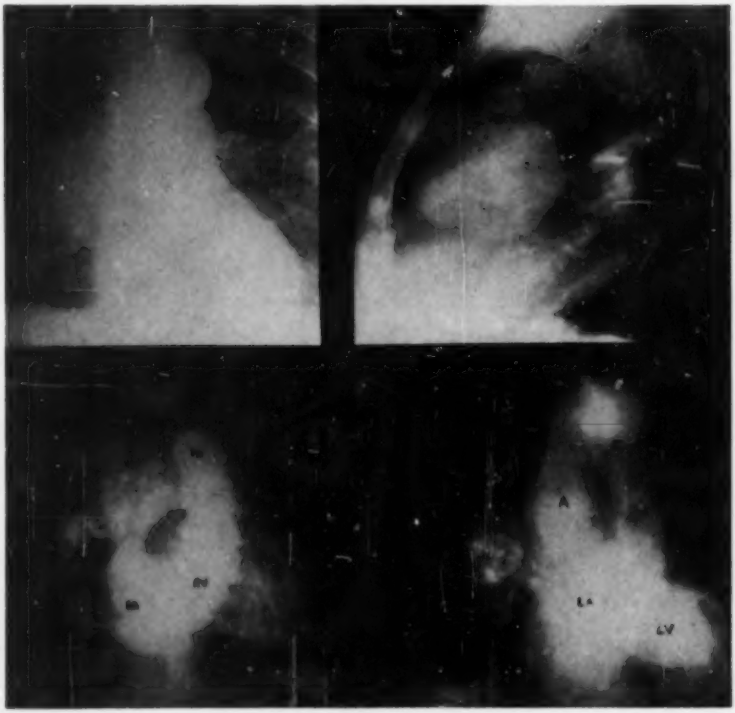

FIGURE 5 (Case 4): Upper left and right: Preliminary films. Large right anterior superior mediastinal mass. Lower left: Angiocardiogram at 2 seconds after antecubital vein injection. Right heart visualization. Mass is extravascular. R.A.—right atrium; R.V.—right ventricle; P.A.—pulmonary artery. Lower right: Left heart visualization at seven seconds. No relation between mass and aorta or left heart. L.A.—left atrium; L.V.—left ventricle; A—aorta.

difficulty in swallowing. Dyspnea was present on climbing two flights of stairs. Occasional dizziness occurred.

She was in an automobile accident the previous year, and was struck in the chest with the steering wheel. There was no fracture.

Physical examination was essentially negative. Blood pressure was 115/85. Serology was negative.

Roentgen examination of the chest showed a mass which could not be separated from the projection of the aortic arch. It was thought to pulsate.

In view of the automobile accident, the possibility of traumatic aneurysm was considered.

Angiocardiography showed good visualization of the right and left heart, pulmonary vessels and aorta. The mass did not opacify.

Conclusion: Non-opacifying mass in close relation to the aorta, but presumably extravascular.

The mass was resected. Found to be a typical bronchogenic cyst.

Case 6: C. M., a 73 year old white man, entered the hospital with a history of hemoptysis for one week. For many years a cough had been present, productive of one half cup of yellowish sputum in 24 hours. Two weeks prior to admission he developed a respiratory infection, manifested by rhinorrhea, fever, and increased cough and expectoration.

Physical examination: Blood pressure was 300/110. There were minimal residual changes from a left hemiplegia five years ago. There was hyper-resonance over both lungs, with coarse rales in the left posterior chest.

Kahn test was doubtful. Multiple sputum examinations for tubercle baciili were negative.

Roentgen examination of the chest, revealed a left hilar mass with linear infiltrations lateral to it. Increased linear markings were noted in the right upper lobe.

Tomographic study of the left hilar showed the bronchus and its branches to be patent. Dilated bronchi could be seen extending almost to the left lateral chest wall.

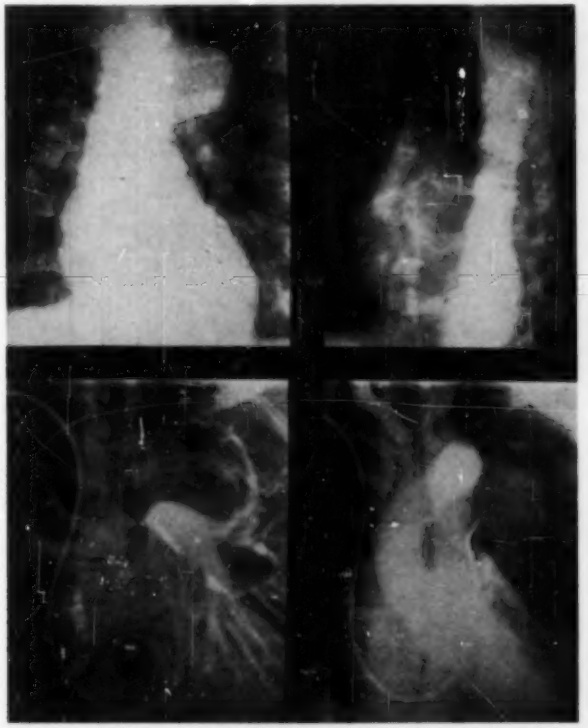

FIGURE 6 (Case 5): Upper left and right: Preliminary films. Mass seems related to posterior portion of aortic arch. Lower left: Two seconds after pulmonary artery injection. Normal pulmonary artery. Branches to left upper lobe show lateral displacement. Lower right: At seven seconds. The left heart and aorta appear normal. No evidence of aortic aneurysm. Surgical findings: bronchogenic cyst.

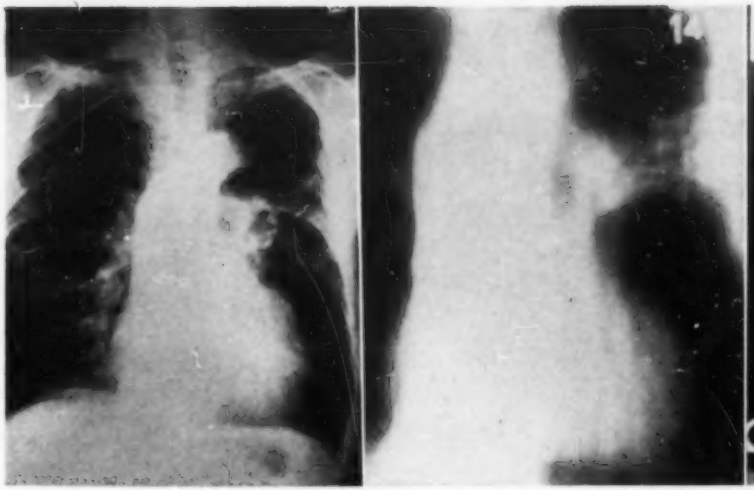

FIGURE 7

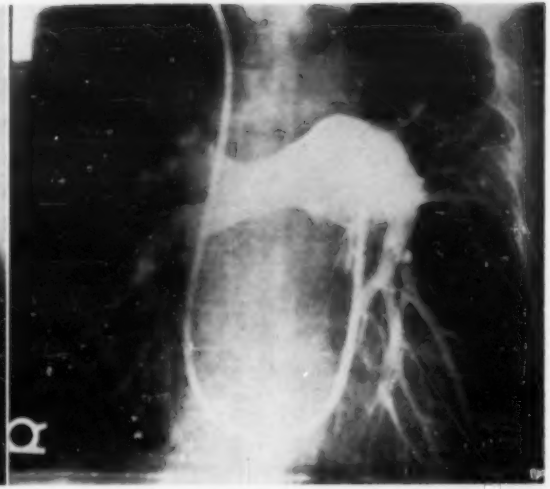

FIGURE 8

Figure 7 (Case 6): Left: Preliminary film. Left hilar mass. Fibrotic changes noted in right upper lobe and left mid-lung field. Right: Tomogram, left hilum. Mass is clearly visualized. Left main bronchus appears patent. Dilated bronchial branches extend to lateral chest wall. Associated fibrosis is noted.—*Figure 8* (Case 6): Two seconds after pulmonary artery injection. Left hilar "mass" is seen to be due to a large main and left pulmonary artery. Diminished vascularity in region of pulmonary fibrosis.—*Conclusion:* 1. Pulmonary fibrosis and bronchiectasis. 2. Associated large main and left pulmonary artery simulating left hilar neoplasm.

Angiocardiography was performed, with injection of the contrast material into the pulmonary artery. The left hilar "mass" is seen to correspond to the left pulmonary artery, which is enlarged.

SUMMARY

1. Angiocardiography was performed on 105 patients using 90 per cent Hypaque.
2. In 38 children, uniformly good visualization was obtained.
3. In 67 adults, good left heart visualization was obtained with equal frequency, after either central or peripheral injection.
4. No serious reactions occurred, and mild reactions were infrequent (26.6 per cent).
5. 90 per cent Hypaque proved to be a safe and successful angiocardiographic contrast medium.

Note: The Hypaque used in this study was generously donated by Winthrop Laboratories.

Addendum: Since the completion of the above study, 90 per cent Hypaque has been used in over 300 additional angiographic examinations, with similar experience as to quality of visualization and infrequency of reactions.

RESUMEN

1. Se llevó a cabo la angiocardiografía en 105 enfermos usando Hypaque al 90 por ciento.
2. En 38 niños se obtuvo un contraste uniformemente bueno.
3. En 67 adultos se obtuvo buena visualización del corazón izquierdo con igual frecuencia ya sea después de inyección central o periférica.
4. No hubo reacciones severas y las reacciones moderadas no fueron frecuentes (26.6 por ciento).
5. El Hypaque al 90 por ciento demostró ser un medio de contraste angiocardiográfico seguro y satisfactorio.

RESUME

1. Une angiocardiographie fut pratiquée chez 105 malades en utilisant l'"hypaque" à 90%.
2. Chez 38 enfants, on obtint uniformément une bonne image.
3. Chez 67 adultes, une bonne mise en évidence du coeur gauche fut obtenue avec une égale fréquence, que l'injection ait été centrale ou périphérique.
4. Il ne survint aucune sérieuse réaction d'intolérance et de faibles réactions furent rencontrées rarement (26,6%).
5. L'"hypaque" à 90% semble être un milieu de contraste angiocardiographique sans danger et satisfaisant.

ZUSAMMENFASSUNG

1. Angiocardiographie wurde bei 105 Patienten vorgenommen unter Verwendung von 90% Hypaque.
2. Bei 38 Kindern kam es zu einer einheitlichen guten Darstellung.
3. Bei 67 Erwachsenen gelang eine gute Darstellung des linken Herzens mit der gleichen Häufigkeit, sowohl nach zentraler wie nach peripherer Injektion.
4. Nennenwerte Nebenreaktionen traten nicht auf, und milde Reaktionen waren selten (26,6%).
5. 90% Hypaque erwies sich als ein sicheres erfolgreiches angiocardiographisches Kontrastmittel.

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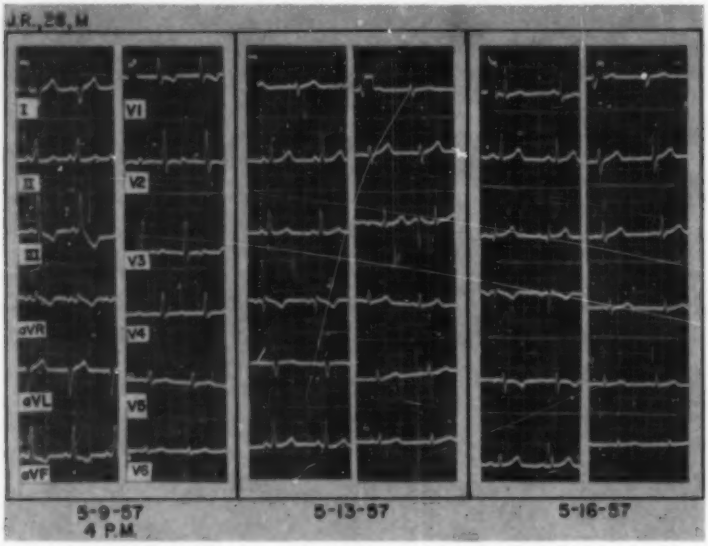
ELECTROCARDIOGRAM OF THE MONTH

The Electrocardiogram in Acute Pulmonary Embolism



These three records are a rather remarkable series depicting the changes in the electrocardiogram due to a pulmonary embolus. This 28 year old man had a right inguinal hernia repair 14 days prior to the record of May 9, 1957. On the night of May 8, 1957, he experienced a sudden substernal pressure and began perspiring. His breath became quite short. His family physician saw him and the initial impression was that he had experienced a coronary occlusion. The next day the electrocardiogram of May 9, 1957 was obtained. The principal changes in this tracing are noted in the marked shift of the mean QRS vector to the right and anterior with a slight widening out of the QRS complex. The P wave itself is not remarkable. A tachycardia is present. A normal transition across the chest does not occur. The T changes suggest the possibility of right ventricular ischemia. (Note that the chest leads are at half standardized).

The next tracing was obtained four days later and at this time the widening out of the QRS complex has disappeared and the mean QRS vector is still to the right but not anterior. An artifact is present in lead V3.

Seven days after the initial tracing, on May 16, 1957, a normal electrocardiogram is recorded with a mean QRS axis at approximately +60 and with the transition zone between lead V2 and V3.

At the time of his admission, the patient's right leg was swollen and palpation in Scarpa's triangle elicited marked tenderness. He was originally treated with anticoagulants, but 13 days after his initial pulmonary embolus, he experienced another episode and an inferior vena cava ligation was done without complications and with full recovery.

E. GREY DIMOND, M.D.

Kansas City, Kansas

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

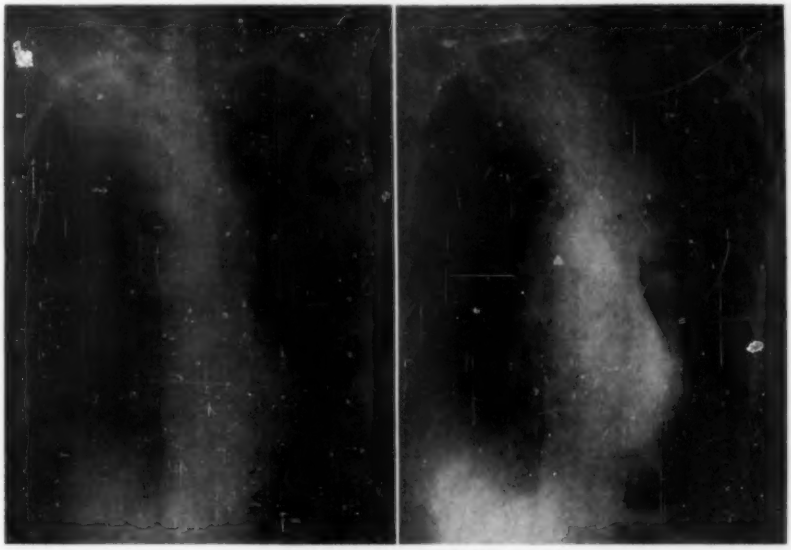
Clinical Information

A colored woman, aged 73, in good health until eight months ago, became dyspnoeic and lost her voice. She experienced dysphagia for two weeks and was able to take only liquid nourishment. The dyspnea related to ingestion of food. She gradually improved. Her voice returned and hoarseness developed. She was married and had three living daughters and admitted having had three still births and five miscarriages.

Physical examination: Facial asymmetry, right facial palsy. Pupils slightly irregular equal and reacted to light and accommodation. Cataracts. Tongue deviated to the right. Neck showed bilateral engorged veins, more marked on right side. The engorged veins extended over the anterior and posterior portions of right upper thorax. Firm stony hard nodule in left lobe of thyroid. Few shoddy cervical glands and matted glands in left axilla. Trachea slightly moveable to the right.

Diminished breath sounds in upper portion of right lung, no rales or rhonchi. Remainder of lungs clear to percussion and auscultation. Heart not enlarged. A 2 greater than P2 with systolic blowing murmurs and base and apex. B. P. 140/94 right, and 160/100 left. Liver slightly enlarged. Neurological examination was negative except for impaired vibratory sensation. Wassermann doubtful, Kline positive.

The x-ray examination revealed a large mass in the anterior and upper third of right hemithorax compressing and deviating the trachea and esophagus to the left. The lower limit of the mass merged with the aorta. Fluoroscopic examination revealed no pulsations. Kymographic examination equivocal.



Clinical Impression

Angiocardiographic examination revealed a large aneurysm of the innominate artery. Tremendous collateral circulation.

HENRY K. TAYLOR, M.D., F.C.C.P.
New York, New York

Case Report Section

Electrocardiographic Changes in Undernutrition

SELIG B. WEINSTEIN, M.D., F.C.C.P.
Oakland, California

The number of people in our world who are chronically undernourished is phenomenal. This number was greatly increased and expanded during World War II and shortly thereafter. General undernutrition is probably the most common metabolic abnormality in the populations of many parts of the world. Although there is a great deal of literature dealing with the problems of undernutrition, especially in the semi-starvation form, as exhibited in the famines of India, China and in the period of World War I and World War II and their aftermath, comparatively few detailed electrocardiographic studies have resulted. Fewer yet are the number that include adequate precordial and limb leads in addition to the standard leads. Naturally the main reason for this deficiency lies in the fact that most of the studies were conducted under adverse conditions and just prior to the popular development of the more recent limb and precordial leads.

Recently the occasion presented itself to observe a patient with severe undernutrition. As far as can be determined from the literature, the electrocardiographic pattern exhibited by this patient had not been previously described.

Case Report

History: A 45 year old white, single, school teacher, entered the hospital complaining of weakness and weight loss. She had been undernourished as a child, and weighed only 98 pounds as a student in high school. During the years 1938 to 1944 she averaged 87 pounds. Her highest weight—120 pounds—was obtained between 1944 and 1946 while in military service. Following discharge her weight once more began to decline and in 1951 she was down to 75 pounds. She had continued to lose weight from then until her admission to the hospital in January 1955. She presented a long-standing history of poor dietary habits. During recent months she experienced episodes of semi-starvation alternating with periods of increased carbohydrate intake. The latter consisted of intermittently (about once every two weeks) gorging herself with carbohydrates usually in the form of about ½ to 1 pound of sugar. This carbohydrate orgy was usually followed by self-induced vomiting and purging. She has had swelling of her feet off and on for about five to eight years. At times she has noted pain in her ankles and legs and more recently has had difficulty in walking due to weakness. Her daily diet consisted of a hot drink for breakfast; a piece of fruit, lettuce, one half cup of milk and cheese for lunch. Vegetables, one piece of toast, and another half cup of milk comprised her dinner. She rounded out the day with an apple and a small amount of cereal in the evening. She had not eaten meat for months and only occasionally did she add an egg to her diet. According to this diet it has been calculated that she averaged 800 to 1,000 calories per day with 45 to 50 grams of protein, 15 to 25 grams of fat, and 90 to 130 grams of carbohydrates. Her diet also contained about 1800 to 2400 Vitamin A units, 0.92 mgs. of thiamine, 1.08 mgs. of riboflavin, 4.63 mgs. niacin and 81 mgs. of ascorbic acids, as well as about 400 units of Vitamin D, about 660 mgs. of calcium, 800 mgs. of phosphorus and 17.1 mgs. of iron. She was having irregular bowel movements with alternating periods of constipation and diarrhea. She attributed this to the fact that she had been taking frequent doses of castor oil whenever she felt that she was "overeating." Her past history revealed that she had numerous colds and pneumonia on five or six occasions. Her menstruation began at age 14, was regular for a number of years, and became grossly irregular 15 years ago. During the past seven years she had failed to menstruate.

Physical Findings: On admission, she weighed 58 lbs. with a height of 62". She was poorly developed, emaciated, pale, almost cadaverous-appearing but in no acute distress.

From the Medical Service, Veterans Administration Hospital.

Mentally she was clear and cooperative. The oral temperature was 96.6°F., a resting heart rate of 72 per minute, and respiratory rate of 18 per minute. The blood pressure was 100/68. The head, neck, abdomen, heart, lungs were normal. There was 4 plus pitting edema of both lower extremities extending from the knees downward. Her skin was cool, dry and atrophic.

All pertinent laboratory tests and x-ray films of the chest were essentially negative. A gastro-intestinal series including small bowel study revealed only hypomotility. An IVP was normal. A bone survey was normal except for mild osteoporosis. The electrocardiogram on admission as noted in Figure 1 exhibited QS complexes in leads V-4 through V-7. A clinical diagnosis of anorexia nervosa with secondary severe undernutrition was made.

Course in the Hospital: She early exhibited marked sensitivity to cold. She kept herself constantly bundled in numerous layers of clothing with windows and doors in her room shut. She was withdrawn, depressed and did not get along too well with other patients and personnel. Her temperature during the first two days of hospitalization ranged between 96.4 and 98°F. and then gradually reached normal and remained so for the remainder of her period of observation. During her early days in the hospital her heart rate ranged between 70-80 per minute. Her weight gradually increased reaching a total of 84 lbs. at the end of eight weeks of hospitalization. The leg and ankle edema cleared and she became less sensitive to cold. The glucose tolerance curve during the ninth week of hospitalization revealed a fasting glucose of 85 mgms. per cent, 155 mgms. per cent at the end of one hour, 135 mgs. per cent at the end of two hours, and 95 mgms. per cent at the end of three hours. She was placed on a course of estrogenic therapy and began to menstruate six days after the drug was discontinued. An electrocardiogram taken at the end of eight weeks of

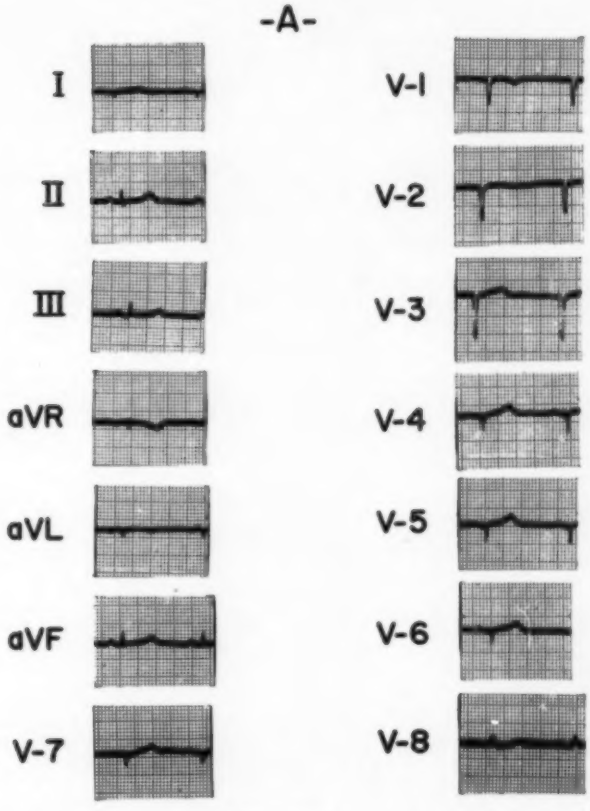


FIGURE 1: ECG taken on admission showing QS complexes in leads V-4 through V-7.

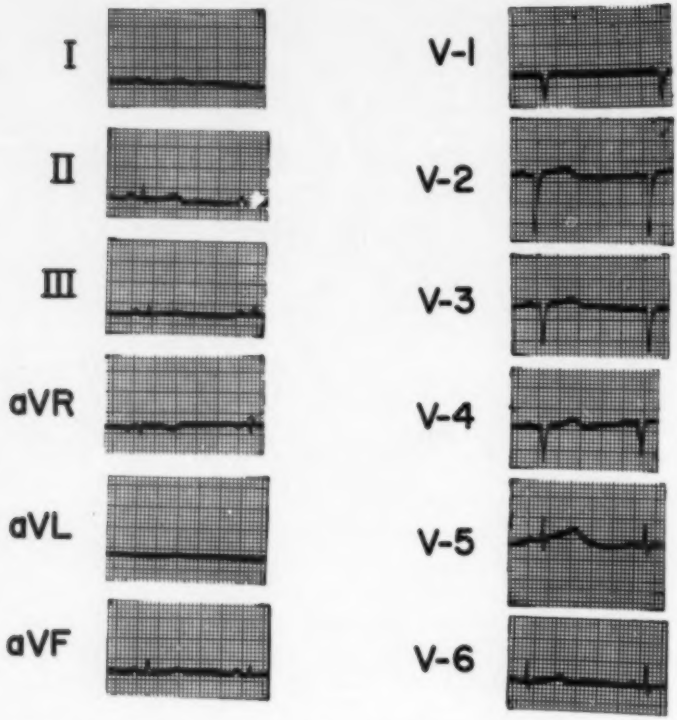


FIGURE 2: ECG taken in eighth hospital week. R waves are now present in precordial leads. The tracing is within normal limits.

hospitalization is shown in Figure 2, and records R waves present in the precordial leads and the tracing is within normal limits. This tracing like the original one (Figure 1) was taken in the usual recumbent position. The degree of emphysema and the position of the diaphragm at this time was unchanged from that noted at the time of admission.

DISCUSSION

In anorexia nervosa the weight loss frequently is as great and sometimes greater than that seen in the non-fatal cases of starvation. War-time starvation and famines present similar pictures of undernutrition. Tur,[1] during the siege of Leningrad (1941-1942) noted sinus bradycardia, right axis deviation and low QRS voltage in patients with severe malnutrition. The T waves were abnormally large in the standard leads, but low or negative in the apical leads. In deteriorating patients, there was a progressive lowering of the T wave amplitude in the standard leads. In another study of 24 cachectic women he noted that the majority had subnormal T wave amplitude in one or more leads, usually in lead 1. The QRS amplitude was subnormal in 12 patients. Out of 15 patients in a better state of nutrition none had right axis deviation and 11 had low QRS and T voltages. During rehabilitation the increase of the T wave amplitude paralleled the clinical improvement and was considered to be of prognostic significance. Cardozo and Eggink[2] found low voltage and sinus bradycardia in 29 cases of severe undernutrition. In addition, the duration of the QR interval was prolonged, absolutely, as well as in relation to their cycle length. Ellis[3] studied the ECG changes in four American prisoners of war, immediately after liberation and during rehabilitation for a period of three weeks. All were severely undernourished and one was almost moribund, having lost about 45 per cent of his body weight. The most prominent feature was a prolongation of the QT interval. He suggested that this prolongation might be due to a prominent U wave which disappeared during the improvement. He also claimed ST segment depression in two patients which in one was associated with an inversion of T2 and T3. All four appeared to show right axis shift which was still in evidence after three weeks of rehabilitation. At this point, however, there was complete disappearance of the QT prolongation, the ST depression, and the T wave changes. Hellerstein,[4] looking at this problem from another point of

view, reported the ECG findings in 16 patients dying with atrophy of the heart. Nine of them showed low QRS voltages and T waves were abnormally low, flat or negative in 11 out of the 16 patients. This being a rare study that included precordial leads, it is interesting to note that he found a low voltage in QRS waves and negative or flat T waves in V-1 to V-5. Sinus bradycardia, however, was not a characteristic feature.

In the Minnesota experiment, Keys et al.[5] reported that their significant changes consisted of a decreased QRS and T wave amplitude, and so agree with Tur and Cardozo and Eggink. They failed, however, to find lengthening of the QT intervals and therefore disagreed with the findings of Ellis and Cardozo and Eggink. Our patient also exhibited low QRS voltage in the standard leads. The striking feature, however, is the presence of QS complexes in V-4 through V-7. An old anterior wall infarct or other intrinsic myocardial pathology such as atrophy was considered in the search for an adequate explanation. Other possibilities included extreme degree of positional changes. None of these, however, completely and adequately explained the findings of the electrocardiographic changes in view of the eventual return to a normal pattern in the period under observation. The ECG changes noted in this patient have never been described in previously recorded reports of patients suffering from severe undernutrition.

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Pulmonary Cryptococcosis*

A Case Report and Experimental Study

M. J. KHAN, M.S., RUTH MYERS, Ph.D. and GRACE KOSHY, M.B., B.S.
Vellore, South India

Cryptococcus neoformans is a widely distributed fungus which occasionally produces systemic mycosis in man. Any part of the body can be involved, but the central nervous system and lungs are most commonly affected.

According to Reilly and Artmann[1] infection with this fungus was first described in 1902 by Forthingham who reported its occurrence in a horse, and in 1906 by Stoddard and Cutler who first reported the disease in man. Webb and Biggs[2] found that out of approximately 220 case reports and studies published, only 14 patients had undergone resection for cryptococcosis of the lung and that so far as was known, on a limited follow-up, 10 had done well. The correct diagnosis had not been made in any case prior to resection. A case of pulmonary cryptococcosis with central nervous system involvement was seen in August 1937 at the Carmichael Hospital for Tropical Diseases in Calcutta as cited by Reilly and Artmann[1] and later diagnosed at the Good Samaritan Hospital in Los Angeles, California.

The Organism and the Disease

Cryptococcus neoformans, a yeast-like organism, is a spherule varying in size from 5-20 microns with a doubly refracting wall and large capsule. It grows well on Sabouraud's glucose agar at room temperature. It has been isolated from trees, flowers, fruits, insects, grasses, and has also been recovered from canned butter and canned milk.[3] It has been isolated from cows with mastitis and horses with pulmonary lesions. Kao and Schwarz[4] have isolated about 41 strains of *Cryptococcus neoformans* from the excreta of pigeons found in the birds' nests. It is rarely pathogenic to man and seems not to be transmitted from man to man or from infected animals to man. Effective immunity has not been demonstrated so far, although some workers have produced antisera in animals[5] which are useful in the study of various strains of cryptococci isolated.

The symptoms of infection depend upon the organs affected. Involvement of the central nervous system is the most constant feature with a clinical picture of meningitis of slow onset. When the lung is affected, the symptoms are usually cough with expectoration, a low-grade fever, mild chest pain, fatigue, weight loss and recurrent attacks of bronchitis. Early roentgenograms, as reported by Greening and Menville,[6] show pulmonary involvement to be greatest at the lung bases. There may be patches of homogeneous consolidation with little surrounding reaction. All of these become confluent with the formation of cavities of varying sizes. Most often a diagnosis of tumor or tuberculoma is made from the skiagram.

*From the Departments of Thoracic Surgery and Bacteriology, Christian Medical College and Hospital.

For specific diagnosis sputum, pus, gelatinous exudates or sediment of centrifuged spinal fluid may be examined by direct smear and culture. Infected materials such as the cerebrospinal fluid can also be injected intracerebrally into mice to recover the fungus. Pathogenicity of isolated cultures should be established by virulence tests.

In some cases a histopathological examination of the surgically resected or autopsy specimen is helpful in establishing the correct diagnosis. In the central nervous system there is chronic leptomeningitis with thickening of the meninges and adhesions to the cortex. There is little exudation but tubercles may be seen scattered through the brain substance. Either a granulomatous perivascular lesion or multiple small nodules, tubercles or gelatinous cyst-like structures scattered throughout the cerebral tissue may be found. Sometimes, even in fatal cases of meningitis, the meninges may appear almost normal. In the lung, the lesion consists of an indurated mass or cavity containing gelatinous matter. There is only slight induration of the pulmonary tissue around it. Microscopic section of the lesion shows numerous organisms in every field.

There is as yet no specific treatment for this infection though many chemicals and antibiotics have been tried with varying success. The first therapeutic agent to be used was potassium iodide, and patients do improve with this. Later sulphonamides were tried with some success. Reilly and Artmann[1] in experiments on white rats found sulphadiazine therapy of some effect. John and associates[7] claimed that of four thiosemicarbazones tested *in vitro*, bromthiazone proved the best. Klingman and Weidman[8] tested fatty acids, napthoquinones, antibiotics and carbamide derivatives and concluded that actidione is the best *in vitro* but that thiocarbonates are best *in vivo*. Wilson and Duryea[9] reported on a patient who had had no apparent recurrence of cryptococcosis for 20 months following a six months' course of actidione with a daily intravenous dose of 40 mgs.

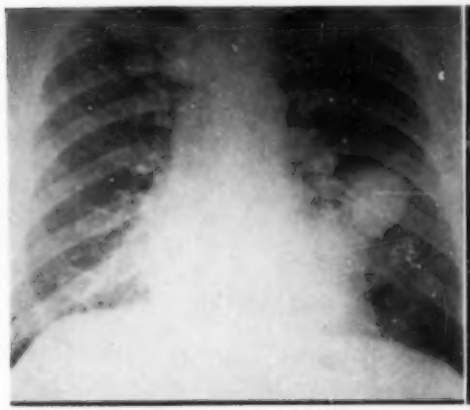

FIGURE 1

FIGURE 2

Figure 1: Roentgenogram of the chest showing a rounded opacity in the left lower lobe.—*Figure 2:* Cut section of the resected lung specimen showing a large rounded circumscribed lesion. Note the cavity in the lesion.

Case Report

Mr. S., a 59-year-old retired man, was admitted on January 3, 1957, in the Department of Neurosurgery for cough with expectoration of five months' duration, and severe frontal headache and low grade fever lasting three months. The fever had been present every day with an evening rise up to 102°F. The headache was not associated with vomiting or nausea. His vision was normal.

He was a clerk by profession and had not worked in any industrial factory or had on any occasion gone out of India. He had been smoking tobacco moderately for the past several years. He had never kept pets like pigeons, etc.

There was no marked abnormality on physical examination except a few rales in the left hemi-thorax anteriorly. A neurological examination did not indicate any lesion in the central nervous system.

Examination of blood revealed a haemoglobin of 13 gms. (Sahli). The erythrocyte sedimentation rate was 30 and 58 mm. at the end of one and two hours respectively (Westergren). His V.D.R.L. test was negative. Lumbar puncture showed the cerebro-spinal fluid to be clear with a pressure of 300 mm. There were 38 white blood corpuscles per cc. with a differential count of polymorphs 22 per cent and lymphocytes 78 per cent. Biochemical analysis of the cerebro-spinal fluid revealed the proteins to be 65 mgs. per cent, chlorides 695 mgs. per cent and sugar 25 mgs. per cent. A smear of the cerebro-spinal fluid was negative for acid-fast bacilli but showed a few yeast-like cells, which also grew in culture. Sputum was negative repeatedly for tubercle bacilli, but culture revealed, besides the usual cocci and bacilli, budding yeast cells.

Skiagram of the skull was normal but that of the chest revealed a dense rounded well defined shadow in the left upper lobe, anterior to the hilum opposite the eighth and ninth dorsal vertebrae (Figure 1).

Bronchoscopy was normal. Endoscopically removed secretions were negative for malignant cells.

Since he was suspected of having pulmonary tuberculosis with involvement of the central nervous system or carcinoma of the lung with a secondary in the brain, he was started on streptomycin and isonicotinic acid hydrazide and was later referred to the Department of Thoracic Surgery.

In spite of the anti-tuberculous drugs, penicillin, aureomycin and quinine, tried at various times, he had a daily evening rise of temperature 102°F. and his condition was deteriorating. At this stage he was suspected of having a tumor and it was decided to do exploratory thoracotomy.

At operation on February 15, 1957, a firm mass about 6 x 3 cms. was palpable in the anterior segment of the left upper lobe. It was not adherent to the chest wall. There were numerous small lymph nodes in the hilum which were soft and not indurated. Frozen section of these nodes did not show tumor. Left upper lobectomy was performed.

Pathological examination of the removed left upper lobe showed a granulomatous lesion in the anterior segment with a cavity, 2.5 cms. in diameter, containing thick, dark-brownish gelatinous material which did not appear caseous (Figure 2). On microscopic study diffuse involvement by small spherical double-contoured structures some of which were free in the alveoli was noted. In other areas there was chronic inflammation, fibrosis and some anthracosis. The outer coat of the spherules stained brilliantly with P.A.S. stain (Figure 3) and were reported by the pathologists as *Cryptococcus neoformans*. Cultures from the resected lesion resulted in a pure growth of *Cryptococcus neoformans*.

His postoperative course was uneventful and a note received seven months after the operation, indicated that he was doing well and had no cough, sputum or headache.

Experimental Study

The pathogenicity of the strain of *Cryptococcus neoformans* isolated from our patient was demonstrated by intracerebral inoculation of a white mouse which died three days later and at autopsy showed adhesion of meninges to skull, with a softening of the brain substance, and also whitish patches on the lungs. Smears and wet preparations of brain and lung tissue revealed the presence of typical encapsulated cryptococci (Figure 4).

It seemed of interest to study the experimental disease resulting from various sites of inoculation; and a group of 16 mice, all male and about five weeks of age, was obtained for this purpose. A four-day culture on a slope of Sabouraud's medium incubated at 37°C was used. Growth was profuse, moist and somewhat confluent. About 5 ml. physiological salt solution was added to the slope and the growth gently rubbed off into it to form a rather dense milky suspension. About 0.05 ml. was used as the

inoculum for each route of inoculation. The animals were divided into four sets, four in each set, then inoculated intracerebrally, intranasally, subcutaneously and intraperitoneally. Light ether anaesthesia was given preceding intracerebral inoculation and intranasal instillation.

From intracerebral inoculation the mice died after 3, 4, 10 and 12 days. Those which survived 10 and 12 days showed marked swelling of the head indicating raised intracranial pressure such as might be found in the human cases simulating brain tumor.[10] Typical encapsulated cryptococci were found consistently in smears of brain and lungs; and metastases to liver, spleen and kidneys were demonstrated by finding the organisms in smears of those organs taken from the animal which died 12 days following inoculation.

Following intranasal inoculation the animals died 35, 40, 43 and 43 days later. Dissemination was demonstrated by the presence of cryptococci in smears from brain, lungs, heart, liver, spleen and kidney. In three of the animals (the fourth had been found only after considerable post mortem change) there were vastly enlarged nodes in the neck showing the presence of the organisms. A constant finding in all four was marked shrinking of liver and spleen and distension of the intestines which were practically devoid of food or fecal matter and bloated with gas. The last of the animals to die was autopsied within an hour of its death. Typical organisms could be found in the organs of these animals but their discovery required at times long search. This seems to be consistent with reports in the literature to the effect that in previously proved cases demonstration of the organisms at autopsy is more difficult when infection has been of long duration.[10-12]

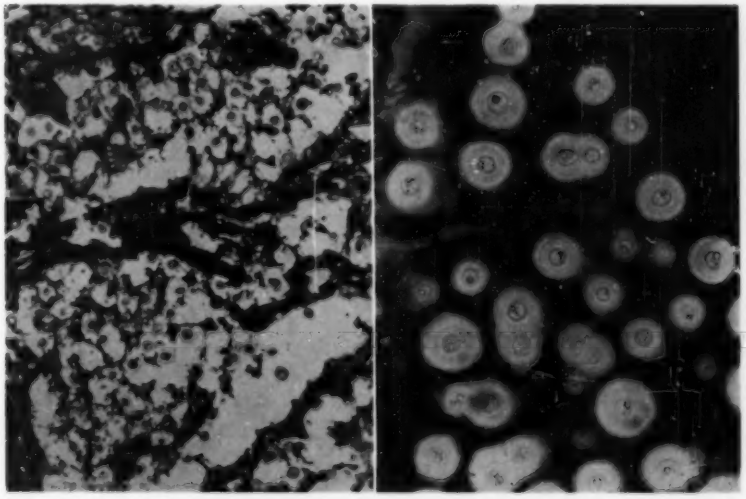

FIGURE 3 FIGURE 4

Figure 3: Microphotograph of a section taken from the resected lung stained with P.A.S. stain showing numerous *Cryptococcus neoformans.*—*Figure 4:* Brain smear from mouse No. 4 which died three days after intracerebral inoculation. Preparation made with India ink and counterstained after drying with saffranin.

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inoculum for each route of inoculation. The animals were divided into four sets, four in each set, then inoculated intracerebrally, intranasally, subcutaneously and intraperitoneally. Light ether anaesthesia was given preceding intracerebral inoculation and intranasal instillation.

From intracerebral inoculation the mice died after 3, 4, 10 and 12 days. Those which survived 10 and 12 days showed marked swelling of the head indicating raised intracranial pressure such as might be found in the human cases simulating brain tumor.[10] Typical encapsulated cryptococci were found consistently in smears of brain and lungs; and metastases to liver, spleen and kidneys were demonstrated by finding the organisms in smears of those organs taken from the animal which died 12 days following inoculation.

Following intranasal inoculation the animals died 35, 40, 43 and 43 days later. Dissemination was demonstrated by the presence of cryptococci in smears from brain, lungs, heart, liver, spleen and kidney. In three of the animals (the fourth had been found only after considerable post mortem change) there were vastly enlarged nodes in the neck showing the presence of the organisms. A constant finding in all four was marked shrinking of liver and spleen and distension of the intestines which were practically devoid of food or fecal matter and bloated with gas. The last of the animals to die was autopsied within an hour of its death. Typical organisms could be found in the organs of these animals but their discovery required at times long search. This seems to be consistent with reports in the literature to the effect that in previously proved cases demonstration of the organisms at autopsy is more difficult when infection has been of long duration.[10-12]

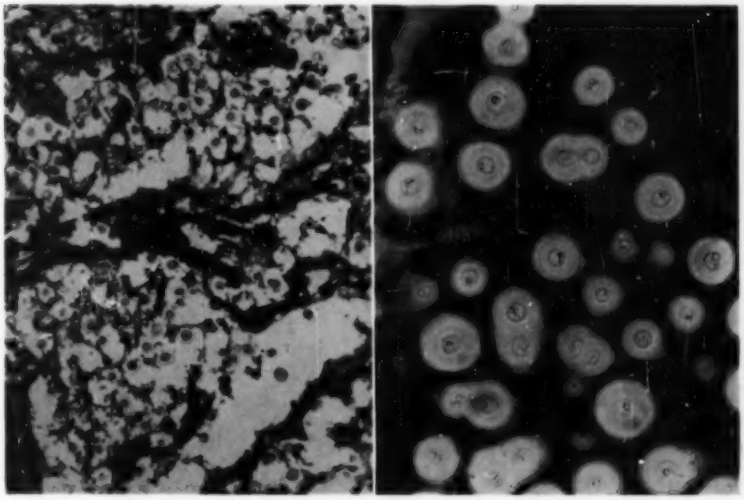

FIGURE 3 FIGURE 4

Figure 3: Microphotograph of a section taken from the resected lung stained with P.A.S. stain showing numerous *Cryptococcus neoformans.*—*Figure 4:* Brain smear from mouse No. 4 which died three days after intracerebral inoculation. Preparation made with India ink and counterstained after drying with saffranin.

The mice which were inoculated subcutaneously, all developed abscesses which grew continuously in size until they burst forming ulcers. They were killed by ether inhalation when it seemed impossible for healing to occur, two after 30 days, the other two after 52 days. The abscess masses were composed of thick gelatinous matter which under the microscope looked like a "pure culture" smear of cryptococci. At autopsy there was no evidence of metastasis.

The final group of mice in the experiment included the four which were inoculated intraperitoneally. One of those died 14 days later but it was felt that the intestinal wall may have been penetrated to some extent since at autopsy one spot showed a slimy yellow exudate containing many cryptococci. Brain smears from this animal were negative, but lung, liver, spleen and kidney smears all contained typical organisms. The second mouse died after 42 days, the third after 59 days with more wide-spread metastasis. In the third, organisms were found in brain, lung, heart, liver, spleen, kidney, omentum and stomach smears, as well as in retrosternal and retroperitoneal lymph node smears, and those from a gelatinous mass on the abdominal wall. At the time of writing, the fourth mouse of this group is still alive 133 days after inoculation. A small subcutaneous nodule, noted first 51 days after inoculation, has gradually but steadily increased in size to a present measurement of about 1 cm. diameter. It is moveable in the tissues. The animal is active and otherwise apparently unaffected by cryptococcal "disease," though infection is obviously present.

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Right Aortic Arch Simulating a Mediastinal Tumor*

A Case Report

ITARU OHARA, M.D.**

Sendai, Japan

Right aortic arch is a developmental anomaly of the large vessels; the aortic arch lies to the right of the trachea and esophagus instead of the left side. It is frequently associated with cardiac malformations, e.g., Eisenmenger complex, 20-25 per cent of Tetralogy of Fallot.[10] The diagnosis of right aortic arch becomes important in relation to surgical treatment. This vascular anomaly has also been known to occur independently without producing noticeable symptoms. Many cases have been discovered accidentally during routine chest examination, because of its unusual mediastinal shadow. Roentgenologically, the following features have been enumerated.[2, 3]

1. On a posteroanterior chest film, a small mass (right aortic knob) is observed below the right sternoclavicular joint occupying an image position of the left aortic knob. No aortic knob is found at the usual site, the first left costosternal joint.

2. The esophagogram in the posteroanterior view will show left displacement of the esophagus at the height of the right aortic knob, while it is pushed forward in the right oblique view.

* Presented at the sixth meeting of the Japanese Circulation Society, the Tohoku-Hokkaido Chapter, Sendai, Japan, June 7, 1958.

**From the Katsura Surgical Clinic, Tohoku University, Faculty of Medicine, Sendai Japan.

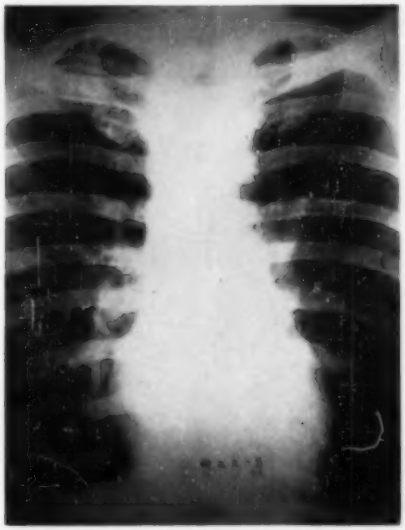

FIGURE 1: K. S. 46 years old, man. Absence of aortic knob below the left sternoclavicular joint.

3. The trachea will show almost an identical displacement as that of the esophagus.

These changes are also caused by mediastinal tumors,[6] e.g., cysts, chondroma, aberrant goiter, lymphoma, aneurysm, exostoses of the sternum, etc., and mistaken for them. If dyspnea or dysphagia is coexisting, careful examination is required for the differential diagnosis.

Generally, the right aortic arch may be classified with those accompanied with the right descending aorta (the so-called right-sided aorta), the left descending aorta and persistent left aortic arch (double aortic arch). In addition to this, the degree of regression of primitive aortic- and branchial arches and the anomalous origin of blood vessels supplying the upper half of the body will cause various displacement and compression of trachea and esophagus from any direction, which will make the interpretation of chest films difficult.[5] Careful examination will become important.

Because of its benign nature, no operation is required for the asymptomatic one despite its false appearance as a mediastinal tumor. Recently, an exploratory thoracotomy was performed for this anomaly without fully recognizing its clinical entity by us.

Case Report

Case Report: H. S., a 46 year old man, was admitted to the University Hospital on March 5, 1958, complaining of heaviness of the neck during swallowing which was accompanied with epigastric distress. He had this symptom during the past two months and lost his appetite. The symptoms, however, ameliorated after receiving two pints of blood by a local doctor. He had no complaint referable to breathing. Barium study of the esophagus was performed at that time which revealed distortion and narrowing of the esophagus. He was referred to us for further examination.

On admission to the hospital, dysphagia had almost disappeared. He was well nour-

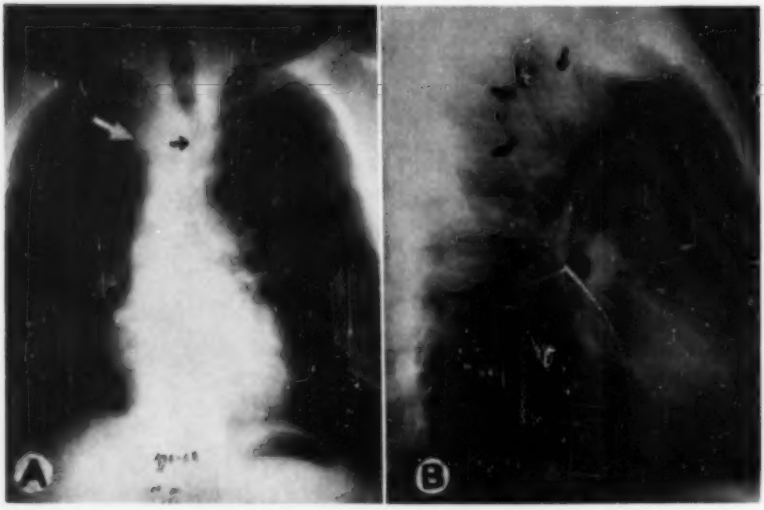

Figure 2: A. Posteroanterior view of the chest taken by a higher voltage. Aortic knob appears below the right sternoclavicular joint (white arrow). Trachea is displaced to the left and slightly stenosed (black arrow). B. Right lateral projection discloses a tumor-like shadow consistent with the level of the aortic arch (black arrows). Trachea is displaced forward (white arrow).

ished and had good appetite. Physical examination was essentially negative. Laboratory studies including electrocardiogram were within normal range. Blood pressure in the right arm was 140-85 mm. Hg., the left 136-72 mm. Hg. Serum Wasserman reaction was negative.

A roentgenogram of the chest in the posteroanterior projection showed no aortic knob in the usual position. A ribbon-like shadow defined the mediastinum on both sides. The pulmonary conus was not dilated (Fig. 1). A heavier penetrated chest film revealed a round, well localized, homogenous mass just below the right sternocostal

FIGURE 3: Right anterior oblique view. The esophagus is displaced forward by the right aortic arch.

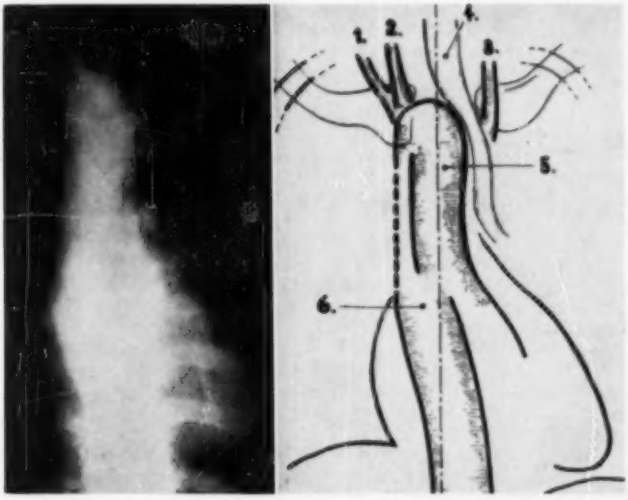

FIGURE 4: Angiocardiogram demonstrates that the aortic arch ascends to the right of the trachea with a right descending aorta. The trachea is displaced to the left and slightly stenosed. 1, 2, 3, 5, and 6, is the right subclavian, the right carotid, the left subclavian, the ascending and descending aorta, respectively. 4, is the trachea.

joint. It slightly displaced the trachea to the left and caused narrowing of the lumen (Fig. 2). In the right lateral view, a mass, measuring 3 x 4 centimeters was visible at the level of the aortic arch, which displaced the trachea slightly anteriorly.

Barium study of the esophagus showed that the esophagus was pushed laterally toward the left with a concave indentation on its right wall in the posteroanterior view, while anteriorly in the right oblique view. Its oral side was slightly dilated but the barium easily descended into the stomach in a normal way. Esophagoscopy disclosed that the upper portion of the esophagus was markedly kinked and stenosed to the left upper direction, 18 centimeters from the teeth, by a pulsating mass. The mucosal pattern was normal. The instrument could not be inserted further due to the small lumen.

The mass causing the esophagus displacement gave the impression of a mediastinal tumor in the upper middle mediastinum.

Exploratory thoracotomy was performed through the right fourth intercostal incision. No tumor was found in the right upper mediastinum. The aorta ascended toward the right side of the spinal column arching over the right bronchus and descended in the right chest. The lower portion of the thoracic aorta traversed the seventh and eighth thoracic vertebrae to the left aortic hiatus. The mass previously thought to be a mediastinal tumor was actually the right aortic arch itself. No pulsating vessel was palpated in front of the trachea.

His postoperative course was smooth. Thoracic aortography was performed on the 14th day with 70 per cent Urokolin via the right cubital vein. The aortogram confirmed the operative finding (Fig. 4). Though the right carotid and subclavian arose from the arch, the course of the left carotid and origin of subclavian artery could not be determined accurately. The possibility is that the subclavian artery may have originated as the last branch from the aortic arch and coursed behind the esophagus.

Discussion

When a chest x-ray film is taken by a conventional method, the right aortic arch may be easily overlooked as in our case if barium study of the esophagus had not been carried out. Absence or hypoplasia of the left aortic knob has been reported in several instances, e.g., persistent left superior vena cava, coarctation of the aorta,[9] etc. In such a case, other symptoms are usually manifest and will not be mistaken for an anomalous aortic arch. A mass in the right upper mediastinum in the absence of the left aortic knob itself have not usually called doctor's attention to consider the possibility of the right aortic arch. This vascular anomaly has misled many doctors to a wrong diagnosis in the past. For instance, according to Garland,[4] an exploratory thoracotomy was performed for the right aortic arch after treating it as a lymphoma with deep x-ray treatment. Bedford and Parkinson[2] reported a 63 year old man who complained of dysphagia with solid food. It was thought to be caused by an intrathoracic goiter and explored to find only a right aortic arch. It has become well known that there are many mediastinal tumors, benign or malignant, which are apparently asymptomatic. Considering the prognosis, in doubtful cases, exploratory thoracotomy is recommended and justified by many surgeons. However, recently, aortography has made it possible to make correct diagnosis preoperatively without subjecting the patients to a distressing procedure.[7, 8] Right aortic arch is the one which should be kept in mind to differentiate from mediastinal tumors.[6]

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Editorial

New Horizons for the Tuberculin Test*

Although the tuberculin test has always had an important place in the diagnosis and control of tuberculosis, recent developments indicate that the test will be even more useful in the decades just ahead. The tuberculosis mortality rate has shown a remarkable drop in the past 10 years, followed by a slower decline in the tuberculosis case rate. An even more significant change in the United States is the diminishing risk of acquiring new infections. In certain areas of the nation, particularly in the Northwest, entire school populations are tuberculin negative. Results of tuberculin testing in Navy recruits provide a broad view for the United States as a whole. In 1950, nine per cent of white recruits were classified as tuberculin reactors. Only seven years later, the proportion of reactors had decreased by one-third. The implication of such findings, substantiated by tuberculin testing programs in various parts of the country, is that new infections with virulent tubercle bacilli must be approaching the low figure of one per 1,000 persons per year.

The complacent attitude, once widely held, that tuberculous infection is an inevitable consequence of attaining adult life is now outmoded, as is the concept that positive reactors are immune and are not likely in the future to develop tuberculous disease. Indeed, current findings demonstrate that most new cases of tuberculosis occur in persons who were infected many years ago. This situation points up the significance of a positive reaction to tuberculin as an indicator of substantial disease risk, and emphasizes the necessity to identify the tuberculin reactors in the population, thus delineating the areas and groups where tuberculosis control efforts can be most effectively applied.

The dramatic change in the tuberculosis infection rate and the constantly diminishing proportion of positive reactors in the population have important implications for medical and public health practice. In differential diagnosis, the pediatrician is no longer the only advocate of tuberculin testing. Now that many adults are negative reactors, the tuberculin test should be a routine part of every examination when pulmonary pathology is suspected.

The method of choice in administering the tuberculin test is the intracutaneous (Mantoux) test. Indeed, it has been well established in numerous trials that a Mantoux test with a dose of tuberculin equivalent to 0.0001 mg. of the international standard purified protein derivative (PPD-S) will produce a reaction in practically all cases of proved tuberculosis with a minimum of false negatives. It is customary in interpreting the test to regard reactions of 6 mm. or more of induration as positive. There is now some evidence, however, that a better dividing point might be 8 or 10 mm., since almost all persons with tuberculosis have reactions this size or larger, and smaller reactions may be nonspecific.

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*Reprinted from *The Journal of the American Medical Association*, 168:894, 1958, with permission of the Editor.

Properly administered and interpreted, the tuberculin test can promptly rule out the tubercle bacillus as the etiological agent in many instances and allow a more diligent and fruitful search for tuberculosis in positive reactors. Wider use of this readily available and inexpensive test should result in a considerable saving of time and money to both patient and physician. The need for the patient to return for a reading of his test may well be a blessing in disguise. All too often, patients with serious pulmonary pathology have only the symptoms and signs of a superimposed acute infection. Obtaining temporary relief, they see no need for a return visit until progression of the underlying disease has become manifest. A test to be read three days later might improve the follow-up of chest diseases seen in office practice.

The continued decline in the proportion of reactors in the population will also increase the usefulness of tuberculin testing for tuberculosis case findings in various community groups. Numerous studies have shown that tuberculosis is heavily concentrated among reactors to tuberculin, particularly among those with the strongest reactions. In many population groups, it is already feasible to offer chest x-rays and other diagnostic procedures only to the small group of positive reactors.

With therapeutic agents which can reverse the infectiousness of nearly all cases, with adequate facilities for isolation, and with the help of the tuberculin test to concentrate diagnostic, case finding, and therapeutic efforts where they will be most effective, the odds against the tubercle bacillus now are greater than ever before. In most areas of the United States today, it should be possible to set our sights not merely for the control of tuberculosis but toward its eradication. As this goal is approached, the identification of the small minority of the population among whom infection still persists will become increasingly important. The tuberculin test can already perform this function with considerable precision, and recent studies indicate that even better testing products and techniques will shortly become available.

The President's Page

THE ART OF LISTENING

Very often in the history of medicine great discoveries seem to come about by some kind of chance. Knowledge which has been available for years and sometimes generations suddenly, almost spontaneously it seems, takes on meaning, and an important medical advance results. Penicillin is a good example. It was first described, and its antibiotic effects at least hinted at, in 1897, by an otherwise obscure French physician, Ernest Duchesne. Fleming, independently, made his notable discoveries in 1928. Yet it was not until 1940 that Florey and Chain utilized his discovery for the benefit of mankind. Similarly the synthesis of isoniazid was reported years before it was used against tuberculosis. Perhaps most of the epoch-making advances in medicine have come about through the particular application of facts already available, however obscurely.

Equally striking in medical history are the discoveries that never did make an impression. One of the more extraordinary practices of our predecessors in medicine was the use of "Setons"—foreign bodies of varying shapes and materials—to induce suppuration in uninfected wounds. The theory underlying this practice was that all illness resulted in one way or another from foreign material in the body; the function of "Setons" was to get it out. Both Paracelsus and Paré reacted violently against this practice and demonstrated in the most public way that "Setons" were harmful and hence that the theory behind their use was unsound. And this happened in the sixteenth century. But there was no follow-up. Physicians came around, gradually, to the Paracelsian view, but the implications of his revolution in the treatment of wounds were not realized until Cohnheim published his fundamental studies in 1867-1873. It is even more painful to realize that the whole conception of sepsis lay agonizingly close to the revolution of Paracelsus and Paré, but it, too, had to wait several centuries.

The fact is, any really fundamental advance in medicine takes a peculiar kind of gift. It requires a mind that can permit an apparently insignificant observation, in the laboratory or in a journal, to reverberate through all of the other facts the mind has in its possession. It requires a peculiar capacity to listen for the faint echoes that such a bit of information may stir in the memory. The rarity of the gift is shown by the way a very vital discovery will be made two or three times before someone comes along who can make the connection between the discovery and the previously known data which gives the discovery its meaning. And sometimes the connection is never made, as in the case of the Paracelsian revolt against Galen's "Setons."

Nor does the opportunity for such reflective listening appear to be greater for us than it has in the past. There are, at the present time, more than 10,000 medical journals being published, containing perhaps 100,000 articles each year. How can the medical profession deal with such a bulk of material reflectively? We can keep up with specialties, perhaps, but progress is not made by keeping up. The piece of information that, being made luminous by reflection, can revolutionize the practice of chest medicine, or heart surgery, or cancer therapy, will not necessarily appear in a journal relevant to these specialties. Chance has always, it seems, operated in medicine—the chance of the right mind to apply a particular facet of information coming across it in the wealth of knowledge that has always been available. As that knowledge increases, the chance of any particular bit of knowledge coming to fruition would seem lessened.

But even more disturbing is the possibility that the fruitful mind itself might be permitted to wane. The discoverer is the person who eternally turns the monologue of the book or article into a dialogue; he asks questions of a set of facts that the author himself never thought of asking. Are we not so dedicated to the pursuit of information and its propagation that we are losing the leisurely habit of reflection? And what will be the consequence of widespread use of audio-visual education and audio-visual communication? A TV set will not stop to be argued with; it demands a posture of utmost submission. And a posture can get to be habitual.

The possibilities for progress in medicine are all around us. A great many questions are being framed in new and exciting ways. But if these possibilities are to be realized we must pay more attention to the creation of an environment favorable to creative thought. We, particularly, need to take to heart the observation of Dr. Inazo Nitobe—"Men have not yet learned what conquests there are in peace and silence."

Seymour M. Farber

Chapter News

PACIFIC NORTHWEST CHAPTER

The annual meeting of the Pacific Northwest Chapter will be held in the Opera House in Sun Valley, Idaho, January 7-9, 1960. The following program will be presented:

January 7

8:00 a.m. Welcome—Kenneth A. Tyler, Gooding, Idaho, Chapter President

Motion Picture Session

"Direct Vision Correction of Mitral Insufficiency using the Heart-Lung Machine"
C. Walton Lillehei and Richard L. Varco, Minneapolis, Minnesota

"Benign and Malignant Tumors of the Trachea and Bronchi"
Paul H. Holinger and Kenneth C. Johnston, Chicago, Illinois

"Surgical Repair of Atrial Septal Defect Utilizing the Atrial Well Technique"
JD Mortensen, Salt Lake City, Utah

9:00 a.m. Scientific Session

"Clinical and Physiologic Changes following Closure of Atrial Septal Defect"
JD Mortensen, L. George Veasy, and Alan Toronto, Salt Lake City, Utah

"Surgical Treatment of Coronary Heart Disease (Report of Animal Investigations)"
J. Karl Poppe, Quentin Quickstad, and Joseph Nohlgren, Portland, Oregon

"Cardiac Catheterization of Infants: Techniques and Relative Importance in Establishing the Diagnosis in Infancy"
Ralph Berg, Jr., and Henry T. Lang, Jr., Spokane, Washington

10.40 a.m. W. R. Rumel, Salt Lake City, Utah, presiding

"The Effect of Heart Rate on Aortic Insufficiency"
Homer Warner and Alan F. Toronto, Salt Lake City, Utah

"Bedside Management of Common, Acute Cardiovascular Problems in the Seriously Ill Postoperative Cardiac and/or Pulmonary Patient—Arrythmias—Hypotension—Pulmonary Edema"
Ralph B. Reaume, Portland, Oregon

Symposium

"Management of Acute Lower Nephron Nephrosis"
Homer Warner, Salt Lake City, Utah

"Steroid Therapy in the Critically Ill Stressed Patient"
Thomas F. Dougherty, Salt Lake City, Utah

"Management of Electrolyte Problems in Seriously Ill Postoperative Cardiac and/or Pulmonary Patients"
Albert Starr, Portland, Oregon

12:15 p.m. Round table luncheon

January 8

8.00 a.m. Edward H. Morgan, Seattle, Washington, Chapter Vice-President, presiding

Motion Picture Session

"Surgical Anatomy of the Pulmonary Hilum"
Franklin R. Smith and E. A. Boyden, Seattle, Washington

"Respiratory Resuscitation Techniques"
Peter Safar, Washington, D.C.

9:00 a.m. Scientific Session

"Extended Resection in Lung Cancer: A Reappraisal and Suggested Plan of Management"
G. H. Lawrence, J. H. Walker, and L. Pinkers, Seattle, Washington

"Permanent Tracheostomy in the Management of Advanced Pulmonary Emphysema"
S. Thatcher Hubbard, Jr., Spokane, Washington

"A New Therapeutic Agent for the Treatment of Bronchial Asthma and its Physiologic Mode of Action"
Ralph Tingey, Salt Lake City, Utah

10:30 a.m. Maurice M. Burkholder, Boise, Idaho, presiding

"The Present Status of Pulmonary Embolism"
Paul F. Miner, Boise, Idaho

"Spontaneous Pneumothorax: Plea for More Aggressive Attitude toward Treatment"
Donald R. Burke, Jr., Seattle, Washington

"Cortico-steroids in Treating Tuberculosis and Sarcoidosis"
H. William Harris, Salt Lake City, Utah

12:15 p.m. Round table luncheon

January 9

8:00 a.m. Lloyd M. Taylor, Great Falls, Montana, presiding

Motion Picture Session

"Radiation: Physician and Patient—The Control of Radiation Exposure in Diagnostic Radiology"
American College of Radiology, U.S. Public Health Service, Rockefeller Foundation

"Flora and Fauna of Connective Tissue—Fun Among the Fibers"
Thomas F. Dougherty, Salt Lake City, Utah

9:30 a.m. Scientific Session

"Mechanisms of Action of Cortical Hormones which Minimize Stress"
Thomas F. Dougherty, Salt Lake City, Utah

"Anomalous Tracheal Lobe—Case Report and Review of Literature"
A. C. Knight, Deer Lodge, Montana

"Xanthine Therapy and Ischial Collosity Prophylaxis"
Speaker to be announced

10:40 a.m. John E. Tuhy, Portland, Oregon, presiding

Symposium on Esophagitis

Medical Aspects—Clarence Pearson, Seattle, Washington

Esophagitis in Pulmonary Disease—Edward H. Morgan, Seattle, Washington

Surgical Treatment—Lucius D. Hill, Seattle, Washington

"Genetic Basis for Isoniazid Metabolism in Humans"
H. William Harris, Salt Lake City, Utah

12:15 p.m. Round table luncheon

For hotel reservations, please write to the Assistant Manager, Sun Valley, Idaho, giving arrival and departure dates.

Obituaries

THOMAS G. HEATON
1900 - 1958

Dr. Thomas G. Heaton, Toronto, Regent for the College in Canada, died at the age of 58 on October 11, 1958. Dr. Heaton, who was born in Goderich, Ontario, attended Appleby College in Oakville, Ontario and the Royal Military College, Kingston. He graduated in medicine from the University of Toronto and was a member of the staff of The Mountain Sanatorium in Hamilton and St. Michael's Hospital, Toronto. During World War II, he served with the Royal Canadian Medical Corps and was chief of medicine at the 13th Canadian General Hospital in England. At the time of his death, Dr. Heaton was a member of the staff of the Chest Clinic of the Toronto Western Hospital and Physician-in-Charge of Tuberculosis, University of Toronto Health Service. He was a past president of the University Medical Alumni Association, a Fellow of the Academy of Medicine of Toronto and a member of the Laennec Society. He is survived by his wife and two daughters.

Samuel J. Forrest, M.D.
Regent for Canada

RAFFAELE PAOLUCCI
1892 - 1958

Professor Raffaele Paolucci of Rome, an Associate Member of the College and one of Europe's leading pulmonary surgeons, died suddenly on September 4, 1958. Professor Paolucci, born in Rome on June 1, 1892, received his M.D. degree from the University of Naples in 1916 and soon became distinguished as a teacher in Italy's leading medical schools. From 1926 until 1930 he was Professor of Surgery at the University of Bari, leaving there to become Director of the Surgical Clinic at the University of Parma and, later the Director of the Surgical Clinic at the University of Bologna. From 1938 until his death, he was Director of the Department of Surgery at the University of Rome. Professor Paolucci was the first surgeon in Italy to perform pulmonary exeresis and the first surgeon in Europe to operate successfully for esophageal atresia and esophagotracheal fistula. He was a pioneer in pulmonary surgery and during the last years of his life, he specialized in cardiovascular surgery.

In addition to his outstanding contributions in the field of surgery, Professor Paolucci was elected a member of the Italian Chamber of Deputies at the age of 29 and was elected to the lower house in 1943. In 1953 he was elected senator, which office he held until his death.

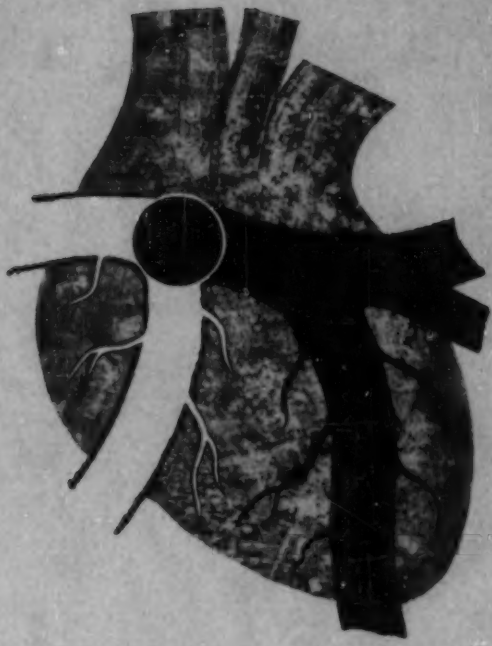
For his bravery in effecting the sinking of the flagship of the Austrian fleet during World War I, Professor Paolucci received the Gold Medal of Military Valor, the highest Italian award, and the United States Navy Distinguished Service Medal.

A. Omodei Zorini, M.D.
Regent for Italy

SIXTO A. FRANCISCO
1891 - 1959

Dr. Sixto A. Francisco of Manila, Philippines, died recently of a heart attack. Dr. Francisco was the former Director of the National Chest Center, Department of Health, Republic of the Philippines. He was a member of the Expert Panel on Tuberculosis of the World Health Organization, Geneva, Switzerland and Secretary-General of the Pan Pacific Tuberculosis Conference, Manila. Dr. Francisco, a Fellow of the College, served as President of the Philippine Chapter in 1954 and was active in College affairs for many years.

Miguel Canizares, M.D.
Regent for the Philippines



"The use of oxygen in myocardial infarction is no longer a desperate or heroic measure. The principle of rest for the heart would require that oxygen be used for the patient who is cyanotic, dyspneic, in shock, in pulmonary congestion or edema, or suffering from a cardiac arrhythmia with rapid heart action. Persisting pain of myocardial infarction may be relieved or reduced by oxygen therapy. In other cases, use of oxygen may well be justified for the first day or two in an attempt to prevent gross anoxia and to compensate for less overt degrees of oxygen deficiency."

—*Early Management of Myocardial Infarction:* B. E. Pollock; Journal of the American Medical Association, 161:404 (June) 1956.

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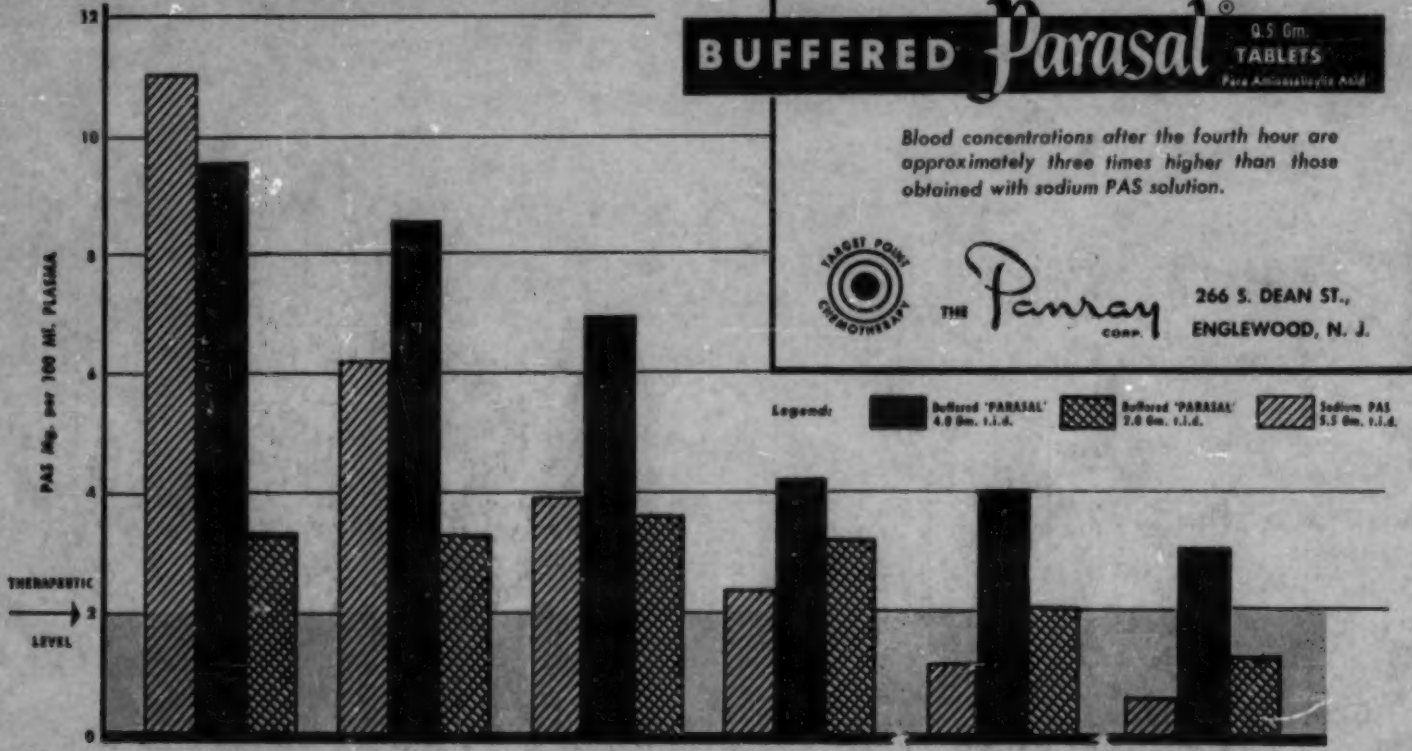

OPTIMUM THERAPEUTIC PAS BLOOD PLASMA CONCENTRATIONS*

Ref.: Deeb, E. N. & Vitagliano, G.R.: A. Rev. Tuber. & Pul. Dis.: 72,543-7 (Oct. '55)

*based on multiple dosages, levels determined after 2nd dose of day.

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